Evidence-based Pediatric Infectious Diseases
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By

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Some books provide comprehensive recommendations without giving the evidence. Some books provide comprehensive evidence without giving any recommendations.

There is a tension between providing useful management recommendations and between providing detailed evidence that allows clinicians to make their own decisions. Books on managing infections, like the excellent Antibiotic Guidelines\(^1\) and the Red Book,\(^2\) give recommendations about which antibiotics to use and the doses, but not the evidence supporting the recommendations. This is deliberate, to keep the books to a manageable length. In contrast, books such as that edited by Virginia Moyer\(^3\) attempt to analyze the evidence for clinical decisions in depth. Sources of summarized evidence, such as the BMJ’s important Clinical Evidence series, provide detailed evidence without recommendations and leave it to the busy clinician to weigh the evidence presented and decide about treatment. While helpful, the depth of the analysis of the evidence means that these sources can deal only with a limited number of clinical situations.

The fundamental principle of the current book is to combine the strengths of both approaches, by analyzing the evidence on management (treatment and, where relevant, diagnosis and prevention) if this is controversial or uncertain, presenting the evidence briefly and then our recommendations about management. The busy clinician can then weigh up the strength of the evidence for our recommendations, and decide how to act. Clinicians can also review the literature themselves, if they have time.

Evidence-based medicine (EBM) has great strengths. For years, many of us thought we were practising EBM, but the best evidence was not easily accessible. That has changed with increasing emphasis on randomized controlled trials, meta-analyses of randomized controlled trials, systematic reviews of the evidence and the rigorous approach to assessing the quality of randomized controlled trials included in the Cochrane reviews, and with the availability of electronic search engines to find the evidence.

Some have espoused EBM wholeheartedly and even, dare one say it, some have advocated it uncritically. It has been fun to satirize this overemphasis on EBM.\(^4\),\(^5\) In reality, EBM has strengths and weaknesses. We should use its strengths while acknowledging its weaknesses.

When evidence is lacking, we still need to decide what to do with our patient. In infectious diseases, do we give antibiotics now or watch carefully? What about adjunctive therapy, steroids, or intravenous immunoglobulin, which might help in critical situations? Reading any of the spate of Practice Guidelines published recently is sobering, because so many of the recommendations are based on “consensus expert opinion” in the absence of good trial data.

In this book we present the evidence for management of many pediatric infectious diseases affecting children in industrialized and developing countries, travelers, and refugees. Our recommendations are based on current evidence about efficacy and safety, but also the likely effects on antibiotic resistance, the costs, adverse effects, ethical and any other relevant considerations.

David Isaacs

References


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DI has been a member of the writing group for the book *Therapeutic Guidelines: Antibiotic* (TGA) from 1994, when the 8th edition was published until now, the 13th edition having been published in 2006. These books are the work of Therapeutic Guidelines Limited, a non-profit-making organization, which publishes evidence-based guideline books on many different areas of medicine. The first edition of TGA was published in 1978, and was the origin of Therapeutic Guidelines Limited. The aim of TGA, then and now, is to promote good antibiotic prescribing, which includes making recommendations that will minimize antibiotic resistance, and also, though less importantly, consider cost as a factor. A committee of experts, drawn from the fields of infectious diseases, microbiology, tropical medicine, general practice, and pharmacology, meets regularly to review the evidence and discuss treatment.

The recommendations in TGA focus almost entirely on antimicrobial use, rather than diagnosis or other aspects of management. While the book you are currently reading has considered the evidence independently of TGA, and also addresses diagnosis and adjunctive therapies, the presentation of antibiotic doses given in boxed format uses an almost identical format to that used by TGA, and we would like to acknowledge this. We have adopted this format, which has evolved over 28 years, because it expresses so clearly and unambiguously which antibiotics should be prescribed and how often. In addition, the actual pediatric doses we recommend are similar but not always identical to those used in TGA. DI would like to acknowledge his indebtedness to his colleagues on the TGA committees for their wisdom and experience, shared so selflessly. While hesitating to single out any one colleague, DI would like particularly to acknowledge Professor John Turnidge from Adelaide, for his advice on antibiotic use in children. DI would also like to acknowledge the staff of Therapeutic Guidelines Limited, notably Jonathan Dartnell and Jenny Johnstone for their expert support and assistance and Mary Hemming for her open support. Therapeutic Guidelines Limited has given permission for us to use their material to help direct our thinking and for us to include some of their antibiotic guidelines, and we gratefully acknowledge their generosity.
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Abbreviations

These abbreviations are used frequently in this book. 

**CI** = Confidence Interval: a way of expressing uncertainty in measurements; the 95% CI tells you that 95% of the time the true value will lie within this range. For example, if you are told that a treatment compared with placebo has a relative risk of 0.50 (95% CI 0.31–0.72) that means the treatment reduces the risk by 50%, and 95% of the time it will reduce the risk by somewhere between 31 and 72%.

**NNT** = Number Needed to Treat: the number of patients you need to treat in order to achieve one extra favorable outcome. For example, if 9 of 10 patients treated with antibiotics for an infection get better compared with 7 of 10 treated with placebo, 2 extra patients get better for every 10 treated and so the NNT is 10/2 or 5.

**OR** = Odds Ratio: the ratio of the odds of having the outcome in the treated group compared to the odds of having it in the control group. For example:
- If 10 of 100 treated patients have persistent symptoms, the odds of persistent symptoms are 10/90 or 0.11 (11%).
- If 30 of 100 untreated/placebo patients in the same study have persistent symptoms, the odds are 30/70 or 0.43 (43%).
- The odds ratio is 0.11/0.43, which is 0.26.

**RR** = Relative Risk or Risk Ratio: the ratio of the risk in the treated group to the risk in the control group. For example:
- If 10 of 100 treated patients have persistent symptoms, the risk of persistent symptoms is 10/100 or 0.1 (10%).
- If 30 of 100 untreated/placebo patients in the same study have persistent symptoms, the risk is 30/100 or 0.3 (30%).
- The relative risk or risk ratio is 0.1/0.3, which is 0.33.

[When the event rate is 10% or lower, the OR and RR are similar. For more common events, the difference between OR and RR becomes wider, with the RR always closer to 1. In general, it is preferable to use RR.]

**RCT** = Randomized controlled trial: participants are randomly allocated to an experimental or control group and the outcome measured.
CHAPTER 1
Evidence-based practice

1.1 Why evidence-based practice?

We all like to think we are practicing medicine based on the best evidence available. However, we sometimes do things in medicine for one or more of the following reasons:

- “It has always been done that way”
- “Everyone does it that way”
- “The consultant says so”
- “The protocol says so”

We tend not to challenge the dogma because we are too busy or because we do not know how to find the evidence or because we think we know the evidence. If doctors are asked what are the main obstacles to them in trying to review the literature, the commonest answers are lack of time, followed by lack of knowledge. However, innovations have made it much easier and quicker to search the literature.

Sometimes the best evidence available for a clinical decision will be a high-quality systematic review of several good RCTs on patients like yours (see Section 1.5, p. 2). At other times, there may be no trials and the only evidence will be from observational studies, such as case series or even case reports. A clinician making the clinical decision will find it helpful to know the strength of the evidence and the degree of uncertainty in making that decision.

Young doctors should be encouraged to challenge dogma and to ask for the evidence supporting management whenever possible. Senior doctors should be quick to ask the young doctors to look it up themselves and return with the evidence. We should all be open-minded enough to accept that our current practices may be wrong and not supported by the evidence.

In the past our attempts to practice in an evidence-based way were hampered by difficulty in getting easy access to the evidence. Literature searches were cumbersome and evidence was rarely presented to us in a convenient or easily digestible way. That is no longer an excuse. Anyone with Internet access has immediate access to the best evidence and can review the recent literature in a few minutes.

The concept of evidence-based medicine (EBM) was developed by Sackett and colleagues at McMaster University in Canada during the 1980s and 1990s. They defined EBM as the integration of the best research evidence with clinical expertise and patient values. Our ability to practice EBM has been enhanced by the development of systematic ways of reviewing the literature and the availability of search engines to find the evidence.

1.2 The Cochrane Library

The Cochrane Collaboration has revolutionized the way we look at evidence. The Cochrane Collaboration was founded in 1993 and named for the British epidemiologist Archie Cochrane. It is an international non-profit-making organization that produces systematic reviews (see Section 1.5, p. 2) of health-care interventions and makes sure they are updated regularly. We consider that a good Cochrane systematic review provides the best available evidence on interventions. This is because a Cochrane review involves a formalized process of finding all published and unpublished studies, assessing their quality, selecting only those studies that meet predetermined criteria, and performing a meta-analysis when possible. A meta-analysis is a way of combining the results from several studies to get an overall mathematical summary of the data.

Cochrane reviews are only about interventions, which often but not always involve treatment. Cochrane reviews on treatment usually include only RCTs because an RCT is the best study design for avoiding bias when assessing treatment. When considering the evidence for any intervention, it is almost always worth
searching the Cochrane Library before looking elsewhere.

A Cochrane review takes on average 700 hours of work, so we are privileged to have ready access to such information, presented clearly in the Cochrane Library. Even if the Cochrane reviewers find no RCTs or only one, the knowledge that there is only scanty evidence on which to base clinical decisions is itself valuable.

The Cochrane Library is free in developing countries and in the UK, where the National Health Service (NHS) pays for it. It requires a subscription in the USA and Australia, but many libraries and hospitals subscribe. Abstracts of Cochrane reviews are available free to all through PubMed. The Web site for the Cochrane Library is http://www.thecochranelibrary.com/.

1.3 Clinical evidence

Another extremely useful resource is Clinical Evidence, which is a collection of systematic reviews from the BMJ. Clinical evidence is free in developing countries and in the UK, where the NHS pays for it. It requires a subscription in the USA, but many libraries subscribe, and it is currently distributed free to US primary care physicians through an American foundation. The Web site is http://www.clinicalevidence.com/.

1.4 Medline and PubMed

PubMed is a means of easy access to Medline, the comprehensive database provided free to all users by the US National Library of Medicine and the National Institutes of Health. It allows access to the abstracts of thousands of publications from many scientific journals. In addition, if when looking at the abstract the journal logo appears on the right side of the screen, clicking the logo often allows free access to the whole paper. The Web site is http://www.pubmed.gov/.

1.5 Hierarchy of evidence

For studies relating to treatment, which will be the most frequent scenario in this book, there is an accepted hierarchy of evidence, based on study design. This is because any studies where patients are not randomly allocated to one or other treatment (randomized) are likely to be affected by bias. This is not to say there is intentional bias. However, in a non-randomized study, the groups may differ significantly. One group may be more severely affected than the other. An example is preadmission antibiotics for suspected meningococcal infection. A cohort study compared the outcome in a non-randomized group of patients with suspected meningococcal infection given preadmission antibiotics to the outcome in patients not given antibiotics. Patients given antibiotics were more likely to die than patients not given antibiotics. It might appear that antibiotics increase mortality, but the patients given antibiotics are likely to have been sicker than those not given antibiotics. Thus there was bias and the groups were not truly comparable. Studies that do not involve randomized patients are sometimes called “observational studies.”

In general, a Cochrane review (see Section 1.2, p. 1) will give better evidence than a non-Cochrane systematic review and so on, although it is important for you to assess the quality of any evidence, including that from Cochrane and non-Cochrane systematic reviews. Weak data can lead to misleading conclusions.

1 Cochrane review: A peer-reviewed systematic review, usually of RCTs, using explicit methods and published in the Cochrane Library’s Database of Systematic Reviews.

[A Cochrane review is only as good as the quality of the studies included. In many reviews, a meta-analysis is possible, summarizing the evidence from a number of trials.]

2 Systematic review (non-Cochrane): A review that systematically searches for all primary studies on a question, appraises, and summarizes them. Systematic reviews that evaluate treatment usually include RCTs rather than other study types.

[The abstracts of non-Cochrane systematic reviews can be found in PubMed under “Clinical Queries,” and the abstracts of good-quality systematic reviews are in the Cochrane Library’s Database of Abstracts of Reviews of Effectiveness.]

3 Meta-analysis: A meta-analysis is a mathematical summary in which the results of all the relevant studies are added together and analyzed, almost as if it had been one huge trial.

4 RCT: Subjects are randomly allocated to an experimental (treatment) group or a control (placebo or different treatment) group and the outcome studied.

5 Cohort study: A non-randomized study of two groups of patients. One group receives the exposure of
interest (e.g., a treatment) and the other does not. The study on preadmission antibiotics for meningococcal infection is an example.

6 Case-control study: Patients with the outcome being studied are matched with one or more controls without the outcome of interest and compared regarding different exposures to look for risk factors for or predictors of the outcome. For example, a group of children with a rare outcome, say tuberculous meningitis (TBM), could be compared with matched controls without TBM with regard to BCG vaccination, contact with TB, socioeconomic factors, etc., to determine factors that appear to protect against TBM (such as BCG) and risk factors (such as contact with TB and possibly socioeconomic status).

7 Case series: Reports of a series of patients with a condition but no controls.

8 Case reports: Reports of one or more patients with a condition.

The hierarchy of evidence of studies does not apply to evidence about etiology, diagnosis, and prognosis: The best evidence about etiology is from large cohort studies or case-control studies or sometimes RCTs. The best evidence about diagnosis is from large cross-sectional studies in a similar population to yours, because the results will be most relevant to your clinical practice. In these studies, the test or tests you are interested in is compared to a reference test or “gold standard.” For example, a new test like polymerase chain reaction for respiratory syncytial virus might be compared to viral culture.

The best evidence about prognosis is from large cohort studies, in a population like yours, followed over time. The no-treatment or placebo groups from large RCTs can provide excellent data on prognosis also.

The hierarchy of evidence is an oversimplification. It is also important to decide how the results apply to your patients. In general, you need to think whether there are biological reasons why the treatment effect could differ in your patients. Often there are more data for adults than children, as in the Cochrane systematic review of sore throat we discuss later. Should you ignore data from adult studies or are these relevant? For example, is the biology of appendicitis so different in adults compared with children that you can learn no relevant information from studies done entirely in adults?

The other question you always need to consider is “What is the baseline risk in my population?” in order to work out how much your particular patient will benefit. For example, how likely is my patient to have prolonged symptoms from acute otitis media, and by how much would this be reduced by applying the relative risk for antibiotic treatment (measured as a relative risk or odds ratio)?

1.6 Searching the literature

The busy clinician will save time by looking for sources of summarized evidence first. If you have access to the Internet, the easiest initial approach is to look first in the Cochrane Library if available (for systematic reviews and RCTs), then in Clinical Evidence if available, and then in Medline via PubMed. If the programs are not already available on your computer, you can find them by going straight to the Web sites http://www.thecochranelibrary.com for the Cochrane Library, http://www.cliniclevidence.com/ for Clinical Evidence, and http://www.pubmed.gov/ for PubMed. The Web addresses can then be saved as favorites.

Framing the question

The next step is to decide on search terms. It will be a lot easier to search the literature if you can frame the question well. Most questions about treatment in this book are framed in the classic evidence-based PICO format, where P = Population, I = Intervention, C = Comparison, and O = Outcome. Suppose you are interested in whether or not antibiotics are indicated for sore throat in children (see Figure 1.1). Framing the question in the PICO format, you ask “For children with sore throats (Population), do antibiotics (Intervention) compared to no antibiotics or placebo (Comparison) reduce the duration of illness or reduce the frequency of complications (Outcome)?”

Searching for a Cochrane systematic review

You type the search terms “tonsillitis child” or “sore throat” or “sore throat child” into the Cochrane Library search window (where it says “Enter search term” in Figure 1.2) and find that there is a Cochrane systematic review by Del Mar et al. The Cochrane reviewers
Frame the question:

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children with sore throat or tonsillitis</td>
<td>Antibiotics</td>
<td>No antibiotics or placebo</td>
<td>Duration of illness or frequency of complications</td>
</tr>
</tbody>
</table>

Search the literature: Cochrane Library: find a Cochrane review of antibiotics for sore throat in adults and children

Assess the evidence:

Results:
- Six patients need to be treated with antibiotics to cure one extra sore throat at day 3
- Antibiotics reduce the frequency of complications
- Antibiotics more effective when patient has group A streptococcal infection
- Difficult to distinguish between adults and children in the studies, and no subgroup analysis of children was possible
- The evidence is most relevant for children 3 years and older, because the benefits of antibiotics will be less for younger children, who are much more likely to have viral infection causing their sore throat

Decide on action:

Decide if your patient is similar to those studied. If your patient is more likely to have group A streptococcal infection, the benefits of starting antibiotics immediately are likely to be greater

Figure 1.1 Answering a clinical question about treatment.

Figure 1.2 The Cochrane Library home page.
include 27 RCTs, perform a meta-analysis, and present conclusions about the benefits and risks of treating sore throats with antibiotics based on current evidence. When you assess the relevance of the Cochrane review to your patient(s), you note that very few of the studies were performed only in children and the studies that include adults and children do not separate them out clearly. This is a common problem when searching the literature for evidence about children. You search the evidence further for variations in etiology and find that case series show a low incidence of group A streptococcal infection and a high incidence of viral infection in children younger than 3 years with tonsillitis. You make a clinical decision for your patient(s) based on your assessment of the literature (see also p. 176).

**Searching for a non-Cochrane systematic review**

If you do not find a Cochrane systematic review, you may find a systematic review in Clinical Evidence. If neither is successful, you may still find a quick answer to your clinical question. For example, you see a patient with hepatitis A. The books tell you to give normal human immunoglobulin to household contacts, but you wonder about the strength of the evidence. When you enter “hepatitis A” into the Cochrane Library search, you get 53 “hits,” but most are about hepatitis B and hepatitis C. You find a Cochrane systematic review on vaccines for hepatitis A, and a protocol for immunoglobulin and hepatitis A but no data. There is nothing in Clinical Evidence on hepatitis A.

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*Figure 1.3* PubMed home page.
You turn to Medline using PubMed to look for a systematic review first. The best way to search rapidly for these is to use the “Clinical Queries” option. When you click “Clinical Queries,” under PubMed services on the left-hand side of the PubMed home page (Figure 1.3), a new screen appears (Figure 1.4). There is an option “Find systematic reviews.” When you enter “hepatitis A” into the box and click “Enter,” you get 77 hits. But if you enter “hepatitis A immunoglobulin,” you get 15 hits, of which the third is a systematic review of the effectiveness of immune globulins in preventing infectious hepatitis and hepatitis A. The systematic review says post-exposure immunoglobulin was 69% effective in preventing hepatitis A infection (RR 0.31, 95% CI 0.20–0.47).10

**Searching for a meta-analysis**

Suppose your search does not reveal a systematic review. For example, you want to know if immunoglobulin can prevent measles. You find no systematic reviews in the Cochrane Library, Clinical Evidence, or PubMed. Your next question is whether there is a meta-analysis. You can look for a meta-analysis in PubMed using the “Limits” option, at the top left hand of the home page screen (Figure 1.3). You enter the search term “measles,” click “Limits,” and a number of options appear. Down the bottom of the page on the left is the heading “Type of Article.” You click “Meta-Analysis,” then click “Go,” and find there are 16 meta-analyses of measles listed, mostly about immunization and vitamin A, but none is relevant to your question.

---

**Figure 1.4** PubMed “Clinical Queries” page.
Searching for RCTs

If there is no systematic review and no meta-analysis, are there any RCTs? The best way to search rapidly for these is to use the “Clinical Queries” option again, but this time use the “Search by Clinical Study Category” option (the top box on Figure 1.4). You note this is already set on “therapy” and a “narrow, specific search,” because these settings automatically find all RCTs, the commonest type of clinical query. When you put in your search term “measles and (immunoglobulin or immune globulin)” and click “Go,” the program comes up with 94 RCTs. Most of the studies are irrelevant and can be ignored (this always tends to be the case). When you scan the titles and the abstracts, only one is helpful, and this shows that post-exposure prophylaxis with immunoglobulin could not be shown to be effective, reducing the risk of infection by only 8% with wide confidence intervals (less than 0–59%) that crossed zero, so the result is not statistically significant. The study does not tell you whether immunoglobulin reduced severity. You conclude that there is no good evidence that giving post-exposure immunoglobulin prevents measles, and you can find no RCT data to say whether or not it reduces severity.

If you find no RCTs, you may need to try different search terms to make sure that it is not because you are asking the wrong question. There is a lot of trial and error in searching the literature and you will improve with practice.

Searching for non-randomized studies

If you use “Clinical Queries” but change from a “narrow, specific search” to a “broad, sensitive search,” this gives you all clinical trials on the topic, not just RCTs.

Searching for questions about diagnosis

You can also use PubMed to search for questions about diagnosis, such as the best tests available to diagnose a condition. It is best to use “Clinical Queries” again, but this time when you get to the “Clinical Queries” page (Figure 1.4) select “diagnosis” before or after entering your search terms. This automatically takes you

<table>
<thead>
<tr>
<th>Question Type</th>
<th>Information Sought</th>
<th>Study Type</th>
<th>Best Source of Evidence</th>
</tr>
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<tbody>
<tr>
<td>Treatment</td>
<td>Comparison of current best practice with a new therapy or comparison of new therapy with placebo</td>
<td>Systematic reviews of RCTs (with or without meta-analysis); RCTs; clinical practice guidelines (if based on a systematic review of the literature and an assessment of the quality of the evidence)</td>
<td>Cochrane Library Clinical Evidence Clinical practice guidelines Medline (PubMed) Evidence-based Web sites</td>
</tr>
<tr>
<td>Baseline risk (frequency)</td>
<td>Disease incidence; or disease prevalence; or frequency of complications</td>
<td>Population-based studies or cohort studies</td>
<td>Medline (PubMed) Review articles Textbooks</td>
</tr>
<tr>
<td>Etiology</td>
<td>Cause of disease</td>
<td>Cohort studies; case-control studies; RCTs when the question is about an adverse effect of an intervention</td>
<td>Cochrane Library Clinical Evidence Medline (PubMed)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Information about the accuracy of a test, its capacity to identify a specific disorder and to distinguish the disorder from other disorders, and the applicability of a test to a particular patient population</td>
<td>The best studies allow an independent blind comparison between the test and the reference (“gold”) standard for diagnosis</td>
<td>Cochrane Library Medline (PubMed)</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Outcomes of disease: short and long term</td>
<td>Cohort studies or no treatment/placebo arm of RCTs</td>
<td>Medline (PubMed) Textbooks</td>
</tr>
</tbody>
</table>
to studies that give specificity (if you stay on “narrow, specific search”) or sensitivity and specificity (if you select “broad, sensitive search”).

Table 1.1 gives a guide to the most likely places to find the evidence you are seeking depending on the type of question. For a more comprehensive description of EBM and its application to clinical practice, we refer you to recent comprehensive but readable books.9,12

The sort of quick search described above should take you 10–15 minutes. You will improve with practice. If you are scared of trying, you will never know how easy and satisfying it is to scan the literature and find quite good evidence you never knew existed.

References

Rational antibiotic use requires accurate diagnosis and appropriate antibiotic use. Antibiotics have radically improved the prognosis of infectious diseases. Infections that were almost invariably fatal are now almost always curable if treatment is started early. Antibiotics are among our most valuable resources, but their use is threatened by the emergence of resistant strains of bacteria. Physicians need to use antibiotics wisely and responsibly. This means that when deciding which antibiotic to use, we need to consider the likelihood that an antibiotic will induce resistance, as well as traditional evidence-based comparisons of efficacy.

2.1 Antibiotic resistance

Antibiotic use selects for antibiotic-resistant bacteria.\(^1\)–\(^3\) This is an example of rapid Darwinian natural selection in action: naturally occurring genetic variants that are antibiotic-resistant are selected by the use of antibiotics which kill off antibiotic-sensitive strains. It occurs in hospitals with the use of parenteral antibiotics\(^1\)–\(^3\) and in the community with oral antibiotics.\(^4\)–\(^5\) When penicillin was first used in the 1940s and 1950s, *Staphylococcus aureus* was always exquisitely sensitive to benzylpenicillin. The antibiotic pressure exerted by widespread penicillin use selected naturally occurring, mutant strains of *S. aureus*, which were inherently resistant to penicillin. Within a very short period of time, most disease-causing strains of *S. aureus* were penicillin-resistant.

Antibiotic resistance is a highly complex subject and many factors drive resistance, including the nature of the antibiotic, the organism, the host, and the environment.\(^6\) What are some of the most important factors leading to antibiotic resistance and what is the evidence that they can be changed?

**Broad- and narrow-spectrum antibiotics**

Broad-spectrum antibiotics might be expected to be more potent selectors of antibiotic resistance than narrow-spectrum antibiotics, and this has indeed proved to be the case in clinical practice.\(^1\)–\(^3\) Furthermore, exposure to broad-spectrum antibiotics can select for resistance to multiple antibiotics. The third-generation cephalosporins (e.g., cefotaxime, ceftazidime, ceftriaxone) have been shown to be associated with resistance to multiple antibiotics, including selection for organisms with inducible resistance (the organisms exist naturally and multiply during antibiotic treatment) and for extended spectrum beta-lactamase (ESBL)-producing gram-negative bacilli. If the cephalosporins are stopped and the “antibiotic pressure” driving resistance is removed, the situation improves. In an important study of neonatal units in the Netherlands, de Man et al\(^1\) showed that empiric therapy using “narrow-spectrum” antibiotics, penicillin and tobramycin, was significantly less likely to select for resistant organisms than using “broad-spectrum” amoxicillin and cefotaxime. The precise distinction between narrow-spectrum and broad-spectrum antibiotics can be debated, but the most obvious distinction is whether prolonged use is associated with the selection of organisms resistant to multiple antibiotics.

On the other hand, the evidence that broad-spectrum antibiotics are a major problem is rather weak. If a broad-spectrum antibiotic is used for as short a time as possible, it is much less likely to drive resistance. The use of antibiotics such as azithromycin, which has a long half-life, is far more likely to cause problems than short-term use of cephalosporins for sore throat. Indeed, when a single dose of azithromycin was given to Australian Aboriginal children with trachoma, the proportion of
children colonized with azithromycin-resistant *Streptococcus pneumoniae* strains increased from 1.9% before treatment to up to 54.5% at follow-up. The evidence suggested that the selective effect of azithromycin allowed the growth and transmission of preexisting, azithromycin-resistant strains.

**Population antibiotic use**

It might seem self-evident that the sheer volume of antibiotic use is important in resistance: if we use more antibiotics in a population, then we ought to be more likely to select for resistant organisms. This might be through taking antibiotics more often, e.g., for upper respiratory tract infections (URTIs), or taking them for longer or at higher dose. It has been very difficult, however, to find evidence to support this theory. A study looking at antibiotic use in different European countries showed a correlation between high rates of antibiotic resistance and high consumption of broad-spectrum, oral antibiotics in the community. Beta-lactam antibiotic use is associated with increased colonization with penicillin-insensitive pneumococci, both at an individual level (children who had recently received a beta-lactam antibiotic were more likely to be colonized) and a population level. Note that the term penicillin-insensitive is used, because pneumococci are often relatively insensitive to penicillin, but not absolutely resistant, so most pneumococcal infections except meningitis can be cured by increasing the dose of penicillin.

There is some evidence that widespread antibiotic resistance is reversible. Nationwide reduction in macrolide consumption in Finland was associated with a significant decline in erythromycin resistance of group A streptococci. A French controlled intervention study showed a modest reduction in penicillin-insensitive pneumococci associated with reducing the number of prescriptions for URTIs, but not with education on dose and duration. On the other hand, there are situations where decreased use of antibiotics has not been associated with a reduction in antibiotic resistance.

**Antibiotic dose and duration**

Intuitively, one would think that the dose and duration of antibiotic use would be an important determinant of resistance. Treatment with sub-optimal doses or for long periods might be expected to select for resistant organisms. Indeed, a French study of antibiotic use in children found that both dose and duration were important. Not only was oral beta-lactam use associated with a threefold increased risk of carriage of penicillin-insensitive pneumococci, but children treated with lower than recommended doses of oral beta-lactam had an almost sixfold greater risk of carriage of these organisms than children treated with the recommended dose. Treatment with a beta-lactam for longer than 5 days was also associated with an increased risk of carriage. The results suggest that either low daily dose or long duration of treatment with an oral beta-lactam can contribute to the selective pressure in promoting pharyngeal carriage of penicillin-insensitive pneumococci.

Relatively long-term use of a quinolone antibiotic like ciprofloxacin has also been associated with the emergence of ciprofloxacin-resistant strains of MRSA and *Pseudomonas aeruginosa*.

A study on the long-term use of prophylactic antibiotics to prevent urinary tract infection found no statistically significant correlation between the emergence of resistant *Escherichia coli* and the consumption of trimethoprim-sulamethoxazole, amoxicillin-clavulanate, and a number of other antibiotics, but did find highly statistically significant correlations between consumption of broad-spectrum penicillins and quinolones and resistance to ciprofloxacin and nalidixic acid. Quinolone consumption was associated with resistance to gentamicin and nitrofurantoin. Strains of *E. coli* with multiple antimicrobial resistance were significantly more common in countries with high total antimicrobial consumption.

**Topical antibiotics**

Sub-therapeutic concentrations of antibiotics select for resistant strains of bacteria in vitro, and there is evidence that inappropriately low doses of oral antibiotics are associated with resistance in vivo (see above, Antibiotic dose and duration). Another situation where sub-therapeutic antibiotic concentrations are likely is the use of topical antibiotics. In practice, the actual antibiotic is important: in a study comparing vaginal antibiotics, topical clindamycin but not topical metronidazole was associated with the emergence of resistant strains. While one study showed that topical ciprofloxacin was superior to framycetin in the short-term treatment of recurrent otorhoea, a recent
report found that 17 children with recurrent otitis treated with topical ciprofloxacin were colonized with multidrug resistant *Pseudomonas* strains. A randomized trial found that selective decontamination of the intestinal tract with antibiotics, a form of prolonged topical treatment, was associated with a significant increase in resistance of *S. aureus* to oxacillin and ciprofloxacin.

**Mucosal penetration**

The factors leading to antibiotic resistance are not always predictable. Sometimes explanations have to be sought for clinical observations. For example, macrolides were found in Spain to be stronger selectors for penicillin-resistant pneumococci than beta-lactam antibiotics. It has been suggested that one explanation could be the greater mucosal penetration of macrolides, although another possible explanation is that azithromycin, the macrolide used, is bacteriostatic for *S. pneumoniae*.

2.2 Combating antibiotic resistance

There are several measures we can use to try to prevent and to reduce antibiotic resistance, a problem that has been with us ever since antibiotics were first used therapeutically. These can be instituted in hospital and in the community.

**Question** | For hospital doctors, do antibiotic restriction policies compared with no policy reduce inappropriate prescribing? Do they reduce antibiotic resistance?

**Literature review** | We found a Cochrane review of 66 studies, which were a combination of RCTs, controlled before and after studies and interrupted time series, of varying quality.

A Cochrane review of interventions to improve hospital prescribing of antibiotics found that interventions mainly aimed at limiting inappropriate prescribing usually led to decreased treatment (81% of studies) and improved microbiologic outcomes, such as antibiotic resistance (75%). Three of 5 studies showed that instituting antibiotic policies was associated with a reduction in the incidence of *Clostridium difficile* diarrhea.

The measures recommended in Box 2.1 follow from the likely mechanisms of resistance described above.

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**Box 2.1 Recommendations on antibiotic use: eight steps to reduce antibiotic resistance.**

1. Do not use antibiotics unless there is good evidence that they are beneficial in this situation
2. Use the narrowest spectrum antibiotic that will work
3. Use antibiotics at the appropriate dose
4. Use one antibiotic unless it has been shown that two or more are superior
5. Use antibiotics for as short as possible
6. Do not use prophylactic antibiotics, unless there is good evidence of benefit
7. Do not use topical antibiotics if possible, or if you must then prefer ones which are not also used systemically
8. Try to prevent infection, through immunization, infection control, and hygiene measures

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**Are antibiotics needed?**

There are many situations where antibiotics are prescribed against all evidence. A classic example is viral URTIs. Repeated studies and one Cochrane review have shown no benefit and often adverse effects from antibiotics given for URTI, yet repeated studies in general practice, private practice, and hospital practice have shown that antibiotics are prescribed for up to 90% of children with viral URTI.

**Narrow versus broad spectrum**

In this book, we will tend to prefer the use of a narrow-spectrum antibiotic to a broad-spectrum antibiotic, particularly for prolonged use in an intensive care setting. This is not merely because of price (broad-spectrum antibiotics are usually much more expensive than narrow-spectrum antibiotics).

It is now widely accepted that education about appropriate antibiotic use is important, both in hospitals and in the community. Hospital antibiotic prescribing often needs reinforcing with more formal mechanisms for ensuring rational antibiotic use, which may involve constraining antibiotic use by rationing it to appropriate situations. By their use of parenteral antibiotics, particularly in oncology and in intensive care, hospitals are major drivers of antibiotic resistance. Policies to restrict important antibiotics, such as vancomycin (to prevent the emergence of vancomycin-resistant enterococci and vancomycin-intermediate *S. aureus*) or carbapenems and third-generation cephalosporins (to try
to prevent selection for extended-spectrum beta-lactamase producing Gram-negative bacilli, ESBL), need to be reinforced with antibiotic approval systems. There are prescriber support systems to help doctors use the most appropriate antibiotics. Electronic databases are increasingly popular. The mere presence of an approval system, however, does not ensure better prescribing, and antibiotic use still requires auditing. Sometimes an audit will even show that antibiotic prescribing deteriorated despite the introduction of an approval system, indicating that more stringent policing of antibiotic use is needed.

On a national basis, some countries are able to limit the use of broad-spectrum antibiotics by having a limit on the number of antibiotics available or a limit on the number whose cost is subsidized by the government.

**Single versus multiple antibiotics**

For a small number of infections, multiple antimicrobials are clearly superior to one, most notably in the treatment of slow-growing organisms with a propensity for resistance, such as tuberculosis and HIV. Some antibiotics should not be used on their own because of the rapid development of resistance through a one-step mutation; e.g., fusidic acid or rifampicin should not be used alone to treat *S. aureus* infections. In general, however, it is better to use one antibiotic rather than two, unless there is good evidence. For staphylococcal osteomyelitis, for example, it is not uncommon for children to be prescribed fusidic acid as well as fluoxetinecillin, although there is no evidence that the combination is better than fluoxetinecillin alone. This risks increased toxicity as well as an increased chance of resistance, without likely clinical benefit.

**Duration**

For some infections, such as osteomyelitis and endocarditis, where tissue penetration is a problem, there is evidence that using shorter courses than those usually recommended is associated with unacceptable rates of relapse. In other situations, such as urinary tract infection, short courses of antibiotics have been shown to be as effective as longer courses. In many situations, there is no good evidence about the optimal duration of antibiotic use, and it is usually considered safe to stop antibiotics once the patient is clinically better. Prolonged antibiotic use without evidence of benefit should be discouraged because of the risk of resistance (see p. 10).

Many doctors now use electronic ordering of drugs, including antibiotics. One danger is that current software systems are more likely to order repeat, computer-generated, antibiotic prescriptions than happens with handwritten prescriptions. Use of computer-generated prescriptions is estimated to result in 500,000 unnecessary prescriptions of amoxicillin, amoxicillin-clavulanate, cefaclor, or roxithromycin annually in Australia.

**Topical antibiotic use**

Because of the risks of inducing antibiotic resistance, topical antibiotics should not be used unless absolutely necessary. Antiseptics such as chlorhexidine may be just as effective. If topical antibiotics are used in situations where benefit has been proved, e.g., for chronically discharging ears, then topical antibiotics that are not used systemically, such as mupirocin or framycetin, are generally preferable to ones, such as quinolones, that are more likely to drive antibiotic resistance.

**Oral versus parenteral**

Some oral antibiotics are extremely well absorbed and can be used as effectively as parenteral antibiotics. Absorption of antibiotics is erratic in the neonatal period, when parenteral antibiotics should be used for serious infections. For some infections, such as endocarditis, high levels of antibiotics need to be maintained and prolonged parenteral therapy is recommended. For osteomyelitis, in contrast, pediatric studies have shown that children can be treated effectively with short courses of parenteral antibiotics followed by long oral courses.

**Prevention**

Immunization against resistant strains of bacteria can help reduce antibiotic resistance. A classic example is the introduction of pneumococcal conjugate vaccines that include the serotypes of pneumococcus, which are most likely to be resistant to penicillin. Use of these vaccines has been associated with a significant reduction in carriage of penicillin-resistant pneumococci.

There is an increased incidence of infections in childcare facilities, often with resistant organisms. Hygiene measures can reduce the incidence of infections and the need for antibiotics.
References


3.1 Infective endocarditis

Clinical features of infective endocarditis

Infective endocarditis is a rare condition, and is rarer in children than in adults.\(^1,2\) The major risk factor for infective endocarditis for children in industrialized countries is congenital heart disease.\(^2\) In developing countries, valve lesions secondary to rheumatic heart disease remain an important risk factor.\(^2\) Long-term central indwelling catheters, particularly intracardiac ones, are also a risk factor, particularly when used to infuse parenteral nutrition. In adults and some adolescents, intravenous drug use is a risk factor. About 10% of children develop infective endocarditis on an apparently previously normal heart valve (native valve endocarditis).\(^2\)

The clinical presentation relates to one of four phenomena: bacteremic (or fungemic), valvulitic, immunologic, and embolic. Most childhood cases of infective endocarditis present indolently (so-called subacute endocarditis) with prolonged low-grade fever and one or more of malaise, lethargy, pallor, weakness, arthralgias, myalgias, weight loss, sweating, and rigors.\(^2\) Splenomegaly and new heart murmurs are the most common signs.\(^2\) Extracardiac manifestations such as petechiae or purpura, which can be raised, hemorrhages, necrotic lesions, Roth spots (retinal hemorrhages), Janeway lesions (macules on the palms or soles), and Osler nodes (tender finger palp nodules) are less common in children than adults.\(^2\) Hematuria and/or abnormal renal function can result from glomerulonephritis or renal infarct. Children may occasionally present with stroke because of rupture of a mycotic aneurysm caused by CNS emboli. Other embolic phenomena (to abdominal viscera or to the heart causing ischemia) occur rarely.\(^2\) Children occasionally present acutely ill from fulminant endocarditis, usually caused by *Staphylococcus aureus*, with high, spiking fevers and rapidly evolving heart murmurs and signs.\(^2,3\)

Many children with endocarditis do not have the classic cutaneous stigmata, and clinical suspicion needs to be high to avoid missing the diagnosis.

Organisms causing infective endocarditis

The major organisms causing infective endocarditis are shown in Box 3.1.

Various studies in children have shown that about 50% of all episodes of infective endocarditis, whether

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The antibiotics and doses recommended in this chapter are based on those in *Therapeutic Guidelines: Antibiotic*, 13th edn, Therapeutic Guidelines Ltd, Melbourne, 2006.
or not associated with congenital heart disease, are caused by so-called viridans or alpha-hemolytic streptococci. These include S. sanguis, S. oralis (or S. mitis), S. salivarius, S. mutans, and Gemella morbillorum (previously S. morbillorum). Members of the S. anginosus group (S. intermedius, S. anginosus, and S. constellatus) are sometimes called the S. milleri group. These latter organisms can cause endocarditis, but are more likely to cause abscesses. The alpha-hemolytic streptococci are usually sensitive to penicillin, although some are relatively insensitive. 2 S. bovis is a non-enterococcal penicillin-susceptible group D streptococcus.

The HACEK group of organisms are fastidious Gram-negative bacilli which are low-grade commensals of the mouth and upper respiratory tract. They virtually never cause bacteremia except in patients with endocarditis. 2, 4, 5

Staphylococci, both S. aureus and coagulase negative staphylococci, are more likely to be associated with indwelling vascular catheters and following heart surgery. S. aureus infection should be suspected in a child who has skin sepsis (boils, pyoderma) as well as endocarditis.

In the newborn and in children with central catheters, particularly if on long-term parenteral nutrition, S. aureus and Candida are the commonest causes of endocarditis. 2, 4, 5

**Diagnosis of infective endocarditis**

**Blood cultures**
The greater the number of blood cultures sent, the greater the yield. 1, 2, 4, 5 Ideally, we recommend sending at least three blood cultures from separate venepunctures from patients with suspected endocarditis before giving antibiotics. 1 This should be possible even in fulminant infection, where it is important to start antibiotics as soon as possible. Once a bacterium has been cultured, the laboratory should be requested to measure the minimum inhibitory concentration (MIC) of the antibiotic which will inhibit growth of that bacterium, because this will guide treatment. 2

**Echocardiography**
The echocardiogram is central to the diagnosis of infective endocarditis. In adults, transesophageal echocardiography (TEE) is more sensitive than transthoracic echocardiography (TTE). 6 No such studies have been published in children. 2 In children, trans-thoracic is generally preferred to TEE, because the quality of images with TTE is relatively good in children 1, 2 and because a general anesthetic may be necessary to obtain a TEE in a young child. TEE may be helpful when ultrasound penetration is poor, e.g., in obese children, muscular adolescents, post-cardiac surgery, and children with pulmonary hyperinflation. 2

**Other tests**
A number of non-specific findings may support a diagnosis of infective endocarditis, but their absence does not exclude the diagnosis. These include anemia, leukocytosis, thrombocytopenia, elevated ESR and acute phase proteins, hematuria, proteinuria, and renal insufficiency. 2

**The modified Duke criteria**

**Question**  | For children with suspected endocarditis are the modified Duke criteria sensitive and specific enough for clinical use?

**Literature review**  | We found two studies comparing the use of the Duke criteria with other diagnostic criteria for children with proven endocarditis. 7, 8

Because of the difficulties in defining endocarditis when clinical signs are absent, diagnostic schemes have been developed. In 1994, a team from Duke University developed the Duke criteria, which classified cases as “definite” (proved at surgery or autopsy), “possible” (not meeting the criteria), or “rejected” because no evidence of endocarditis was found or another diagnosis was far more likely. 7 Subsequently, the Duke criteria have been modified so that “definite” cases include clinically diagnosed cases, with positive blood cultures with characteristic organisms and echocardiographic evidence, as well as pathologically diagnosed cases. 9 The modified Duke criteria take into account that some organisms, such as the HACEK group of fastidious Gram-negative bacilli, virtually never cause bacteremia unless the patient has endocarditis, whereas others such as S. aureus may cause bacteremia with or without endocarditis. 3 The modified Duke criteria are recommended as the main basis for diagnosis in adults, 1, 10 and a simplified summary is given in Box 3.2.
Box 3.2 Simplified version of modified Duke criteria for definition of infective endocarditis.1.9

Pathologic criteria
Microorganisms by culture or histology from a vegetation or intracardiac abscess
or
Vegetation or intracardiac abscess confirmed histopathologically

Clinical criteria
Definite: 2 major; or 1 major + 3 minor; or 5 minor criteria
Possible: 1 major + 1 minor; or 3 minor criteria
Major criteria:
a. Blood culture grows typical microorganisms from two or more separate specimens
b. One blood culture positive for Coxiella burnetii or positive serology for C. burnetii
c. Echocardiogram positive
Minor criteria:
a. Predisposing feature (heart condition, IV drug user)
b. Fever
c. Vasculitic or other embolic or hemorrhagic clinical features, e.g., Janeway lesions
d. Immunologic phenomena, e.g., nephritis, Osler’s nodes, Roth spots
e. Blood culture positive, but not enough to meet major criterion above
Rejected: Does not meet criteria for possible infective endocarditis and/or firm alternate diagnosis

The modified Duke criteria have been evaluated in children and compared to preexisting criteria, the von Reyn7 and Beth Israel criteria.8 In these studies, children with proven endocarditis were assessed retrospectively to see if they fulfilled Duke9 or modified Duke criteria.10 All 149 children fulfilled Duke criteria for definite or possible infection and none was rejected by Duke criteria, although some cases were missed using the older criteria.7,8 We conclude that the modified Duke criteria have good sensitivity and specificity for endocarditis in children. However, the modified Duke criteria were developed for epidemiologic comparisons and for clinical research. They are a clinical guide for diagnosis, and a clinician may judge that it is wise to treat a child for endocarditis even if the child does not meet the Duke criteria. The decision to treat may be appropriate even if the risk of the child having endocarditis is relatively low, if the consequences of missing the diagnosis would be disastrous.

Treatment of infective endocarditis

Surgery for infective endocarditis
Reviews1.2 have reported echocardiographic features that suggest surgical intervention should be considered, although these are based on expert opinion rather than controlled trials (see Box 3.3).

Antimicrobials for infective endocarditis
The general principles of the antimicrobial treatment of infective endocarditis are that the dose should be high enough and duration long enough to sterilize the heart valves. Organisms in vegetations are embedded in a fibrin-platelet matrix and exist in very large numbers with a low metabolic rate, all of which decreases susceptibility to antimicrobials.2 It is recommended that treatment is given intravenously for the entire duration of each antibiotic course, except for occasional very rare infections, like Q fever. Oral antibiotics have only ever been studied in adult IV drug users with right-sided endocarditis, and the results cannot be extrapolated to children. They are not recommended in children because of concerns about achieving adequate blood levels with oral treatment.1,2

For fulminant infections, infections of prosthetic valves, and persistent infections, we recommend consulting a cardiovascular surgeon.

Box 3.3 Echocardiographic features indicating possible need for surgery.1.2

Vegetation
Persistent vegetation after systemic embolus or emboli
Large vegetation of anterior mitral leaflet (particularly > 10 mm)
Increasing size of vegetation
Valve
Acute aortic or mitral regurgitation with heart failure
Resistant heart failure
Valve perforation, rupture, dehiscence, or fistula
Endocardium
New heart block
Large abscess
Question | For children with infective endocarditis is any one antibiotic regimen more effective than others?

Literature review | We found one small non-randomized study in children. We found six RCTs in adults, five of staphylococcal endocarditis and only one of streptococcal endocarditis. We found one meta-analysis of the role of adding aminoglycosides to a beta-lactam. We found treatment guidelines for adults and children based on best available evidence and expert consensus where evidence was not available.

We found no useful data for children. The only study was a non-randomized study of 10 children who received cefotaxime plus an aminoglycoside compared with 10 children who received different beta-lactams plus an aminoglycoside for longer time. The outcome was equivalent.

In adults, the data were also very limited. A meta-analysis of four RCTs and one retrospective study involving 261 patients did not find that the addition of aminoglycosides to a beta-lactam improved outcome. However, the quality of the studies was weak, and the confidence intervals wide. In the only RCT of the treatment of penicillin-susceptible streptococcal endocarditis, once daily ceftriaxone for 4 weeks was equivalent to 2 weeks of ceftriaxone plus gentamicin.

For short course therapy for right-sided S. aureus endocarditis in intravenous drug-users, cloxacillin alone was as effective as cloxacillin plus an aminoglycoside.

The current recommendation for the initial empiric treatment of endocarditis is to use once-daily dosing of gentamicin, in case the patient has Gram-negative sepsis, pending blood culture results. If endocarditis is subsequently proven to be streptococcal or enterococcal, thrice-daily low-dose gentamicin is often recommended for synergy, although the evidence is weak. For the antibiotic regimens recommended below are, therefore, based mainly on expert opinion.

Empiric treatment of endocarditis, unknown organism

For empiric therapy to cover streptococcal, staphylococcal, and Gram-negative endocarditis, we recommend:

- benzylpenicillin 60 mg (100,000 U)/kg (max 2.4 g or 4 million U) IV, 4-hourly PLUS
di/flucl/oxa/nafcillin 50 mg/kg (max 2 g) IV, 4-hourly PLUS
gentamicin <10 years: 7.5 mg/kg; ≥10 years: 6 mg/kg IV, daily OR
gentamicin 2.5 mg/kg IV, 8-hourly

We recommend initial empiric therapy using vancomycin and gentamicin in any of the following circumstances:
- prosthetic cardiac valve;
- hospital-acquired infection;
- anaphylactic penicillin allergy;
- community-associated MRSA (cMRSA) infection suspected on epidemiologic grounds, such as ethnicity, although skin and soft tissue infections due to cMRSA are far more common than endocarditis.

When using vancomycin, we recommend:

- vancomycin 12 years or older: 25 mg/kg (max 1 g); child <12 years: 30 mg/kg (max 1 g) IV, 12-hourly PLUS
gentamicin <10 years: 7.5 mg/kg; ≥10 years: 6 mg/kg IV, daily OR
gentamicin 2.5 mg/kg IV, 8-hourly

Streptococcal endocarditis due to highly penicillin-sensitive organisms

Viridans streptococci are usually highly susceptible to benzylpenicillin (defined as MIC ≤0.12 mg/L). The MIC for penicillin should be measured, as this determines treatment. Low-dose aminoglycoside is added for synergy.

For uncomplicated endocarditis due to streptococci which are highly susceptible to benzyl penicillin (MIC ≤0.12 mg/L), we recommend:

- gentamicin 1 mg/kg IV, 8-hourly for 14 days
PLUS EITHER
- benzylpenicillin 45 mg (75,000 U)/kg (max 1.8 g or 3 million U) IV, 4-hourly for 14 days OR
ceftriaxone 100 mg/kg (max 4g) IV, 24-hourly for 14 days
[NB: For low-dose 8-hourly synergistic dosing, measure only trough levels and keep level <1 mg/L to minimize toxicity (see Appendix 2).]

Alternatively, as a single drug, use:

- **benzylpenicillin 45 mg (75,000 U)/kg (max 1.8 g or 3 million U) IV, 4-hourly OR ceftriaxone 100 mg/kg (max 4g) IV, 24-hourly for 4 weeks**

Adults at low risk for severe disease may be managed successfully as outpatients after initial inpatient therapy (usually for at least 1 to 2 weeks), although use of an established outpatient intravenous antibiotic therapy program is recommended. For suitable patients, a proven treatment course is ceftriaxone 2 g IV daily to complete a 4-week course. Limited evidence supports the use of a continuous infusion of benzylpenicillin to treat adults at home using the same total daily dose as intermittent therapy outlined above. Such management in children should only be contemplated in special circumstances.

For **complicated endocarditis** (large vegetation, multiple emboli, symptoms longer than 3 months, secondary septic events), we recommend treatment in hospital with:

- **benzylpenicillin 60 mg (100,000 U)/kg (max 2.4 g or 4 million U) IV, 4-hourly for 4 weeks PLUS gentamicin 1 mg/kg IV, 8-hourly for 14 days**

[NB: For low-dose 8-hourly synergistic dosing, measure only trough levels and keep level <1 mg/L to minimize toxicity (see Appendix 2).]

**Streptococci relatively resistant to benzylpenicillin (MIC >0.12 to ≤0.5 mg/L)**

For endocarditis due to streptococci relatively resistant to benzylpenicillin (MIC >0.12 to ≤0.5 mg/L), we recommend:

- **gentamicin 1 mg/kg IV, 8-hourly for 14 days PLUS EITHER benzylpenicillin 60 mg (100,000 U)/kg (max 2.4 g or 4 million U) IV, 4-hourly for 4 weeks OR ceftriaxone 100 mg/kg (max 4 g) IV, 24-hourly for 4 weeks**

[NB: For low-dose 8-hourly synergistic dosing, measure only trough levels and keep level <1 mg/L to minimize toxicity (see Appendix 2).]

**Streptococci resistant to benzylpenicillin (MIC >0.5 to <4 mg/L)**

To treat endocarditis due to streptococci resistant to benzylpenicillin, follow the treatment recommendations for penicillin-susceptible enterococcal endocarditis (see enterococcal endocarditis, below).

The susceptibility of **Abiotrophia defectiva, Granulicatella** (previously called nutritionally variant streptococci), and **Gemella** species is often difficult to determine and unreliable. They should be treated as for enterococci (see below).

**Streptococci highly resistant to benzylpenicillin (MIC ≥4 mg/L)**

There is no established regimen for endocarditis due to highly benzylpenicillin-resistant streptococci (MIC ≥4 mg/L). Animal data and case reports favor the use of the following regimen:

- **vancomycin <12 years: 30 mg/kg (max 1 g) IV, 12-hourly, 12 years and older: 25 mg/kg (max 1 g) IV, 12-hourly PLUS gentamicin 1 mg/kg IV, 8-hourly for 4 weeks**

[NB: For low-dose 8-hourly synergistic dosing, measure only trough levels and keep level <1 mg/L to minimize toxicity (see Appendix 2).]

**Enterococcal endocarditis**

Organisms such as **Enterococcus faecalis** and **Enterococcus faecium** are relatively difficult to treat with penicillin, even when reported to be susceptible to penicillin (MIC 0.5–2 mg/L). It is always recommended to give concomitant gentamicin for optimal bactericidal activity, although there are no studies. Antibiotic resistance is an increasing problem. All isolates should undergo testing for penicillin MIC and high-level aminoglycoside resistance. Enterococci are inherently resistant to third-generation cephalosporins, which should not be used to treat them.

For susceptible infections, use:

- **gentamicin 1 mg/kg IV, 8-hourly for 6 weeks PLUS EITHER benzylpenicillin 60 mg (100,000 U)/kg (max 2.4 g or 4 million U) IV, 4-hourly for 6 weeks OR amoxi/ampicillin 50 mg/kg (max 2 g) IV, 4-hourly for 6 weeks**
Cardiac infections

[For low-dose 8-hourly synergistic dosing, measure only trough levels and keep level < 1 mg/L to minimize toxicity (see Appendix 2).]

For patients with short-term symptoms (<3 month) the duration of treatment may be shortened to 4 weeks.1,2

For aminoglycoside-sensitive enterococci with high-level penicillin resistance, we recommend:

vancomycin <12 years: 30 mg/kg (max 1 g) IV, 12-hourly, 12 years and older: 25 mg/kg (max 1 g) IV, 12-hourly PLUS gentamicin 1 mg/kg IV, 8-hourly for 4 weeks

[For low-dose 8-hourly synergistic dosing, measure only trough levels and keep level < 1 mg/L to minimize toxicity (see Appendix 2).]

For enterococci with high-level aminoglycoside resistance, we recommend seeking advice on alternative regimens and considering surgery.1,2 Vancomycin-resistant enterococci usually exhibit penicillin and high-level aminoglycoside resistance. Treatment is recommended with combination regimens including linezolid and/or quinupristin+dalfopristin, often with surgery.17

**Staphylococcus aureus endocarditis**

*S. aureus* endocarditis is significantly more common in perioperative endocarditis, in cyanotic patients and in infants < 1 year old.4 At present, almost all community-acquired *S. aureus* endocarditis is susceptible to methicillin, while cMRSA tend to cause soft tissue infections but not endocarditis. However, community-associated MRSA may become more virulent, and cMRSA endocarditis may become more common. Surgery is often needed and we recommend early consultation with a cardiac surgeon.

For methicillin-susceptible staphylococci, we recommend:

di/flucl/oxa/nafcinil 50 mg/kg (max 2 g) IV, 4-hourly for 4–6 weeks

Routine coadministration of gentamicin (as for streptococcal endocarditis) is not supported by evidence14 and is not recommended.

Four weeks of therapy appears to be sufficient in uncomplicated cases,2 including in intravenous drug users (IVDU) with right-sided endocarditis, but at least 6 weeks is recommended for complications, such as perivalvular abscess, osteomyelitis, or septic metastatic complications.16

For methicillin-resistant staphylococci, we recommend:

vancomycin <12 years: 30 g/kg (max 1 g) IV, 12-hourly, 12 years and older: 25 mg/kg (max 1 g) IV, 12-hourly

*S. aureus* with intermediate susceptibility to vancomycin have been described (vancomycin-intermediate *S. aureus*, VISA). Successful treatment with linezolid has been described in case reports,18,19 but experience is limited.

**Endocarditis caused by the HACEK group**

The HACEK group of oral Gram-negative bacilli (see Box 3.1) often grow poorly on traditional culture media and may require specialized microbiologic techniques. Although many strains are susceptible to penicillin, susceptibility testing may be difficult, and the HACEK group should be treated as if they are penicillin-resistant.1 We recommend:

ceftriaxone 50 mg/kg (max 2 g) IV, daily for 4 weeks OR
cefotaxime 50 mg/kg (max 2 g) IV, 8-hourly for 4 weeks

**Cat scratch endocarditis**

For cat scratch endocarditis, we recommend:

doxycycline >8 years: 2.5 mg/kg (max 100 mg) orally, 12-hourly for 6 weeks PLUS EITHER gentamicin 1 mg/kg IV, 8-hourly for 14 days OR rifampicin 7.5 mg/kg (max 300 mg) orally, 12-hourly for 14 days

[For low-dose 8-hourly synergistic dosing, measure only trough levels and keep level < 1 mg/L to minimize toxicity (see Appendix 2).]

**Prosthetic material endocarditis**

The mortality of endocarditis involving prosthetic material is high, particularly when infection is with *S. aureus*. Observational studies in adults suggest mortality rates may be decreased with a combined medical–surgical approach, using early replacement of infected valves or synthetic material.20–22
For empiric therapy, until a definitive diagnosis is made, we recommend:

- **vancomycin**
  - <12 years: 30 mg/kg (max 1 g) IV, 12-hourly
  - 12 years and older: 25 mg/kg (max 1 g) IV, 12-hourly PLUS
- **gentamicin**
  - <10 years: 7.5 mg/kg; ≥10 years: 6 mg/kg IV, daily OR gentamicin 2.5 mg/kg IV, 8-hourly

[NB: See Appendix 2 for advice on the prolonged use of gentamicin.]

### Endocarditis caused by other bacteria

Endocarditis may rarely be caused by other bacteria. Non-toxin-producing strains of *Corynebacterium diphtheriae* (i.e., diphtheroids, not diphtheria-causing strains) are frequent contaminants of blood cultures, but can also cause endocarditis, including in children. *Neisseria gonorrhoeae* is another uncommon cause of endocarditis. *Pseudomonas aeruginosa* and Gram-negative enteric bacilli (other than HACEK) are rare causes of endocarditis that usually requires prolonged therapy for at least 6 weeks and sometimes surgery.

### Fungal endocarditis

Fungal endocarditis is rare, occurring mostly in neonates, immunocompromised patients with indwelling catheters, and children on long-term parenteral nutrition through a central catheter. Medical therapy alone is usually unsuccessful, and most patients need surgery as well as antifungal agents. We recommend:

- **amphotericin B deoxycholate** 1 mg/kg IV daily PLUS
- **flucytosine (5-FC)** 25 mg/kg (max 1g) orally, 6-hourly (if susceptible)

Liposomal amphotericin may be considered in patients with moderate to severe renal impairment or unacceptable infusion-related toxicities.

Amphotericin B remains the first-line antifungal agent for medical therapy, although it does not penetrate vegetations well. Although the imidazoles, such as fluconazole, have no proven efficacy in human fungal endocarditis, long-term suppressive therapy with fluconazole could be considered for patients with susceptible organisms who are not able to undergo curative surgery.

### Culture-negative endocarditis

Endocarditis may be culture-negative because of prior antibiotic therapy or when caused by one of a number of microorganisms, such as *Bartonella* species (including *B. henselae* which causes cat scratch disease), *C. burnetii* (Q fever), *Legionella* species (in adults), or fungi, including *Candida albicans*. Molecular methods, such as polymerase chain reaction for microbial 16S ribosomal RNA genes and sequencing of the product, may allow a specific organism to be identified.

Patients with culture-negative endocarditis should be treated empirically with benzylpenicillin plus gentamicin, as for enterococcal endocarditis (see p. 18) unless there is a strong reason to suspect an alternate diagnosis such as Q fever or fungal infection. In a retrospective review of 348 culture-negative endocarditis cases referred to a French reference center, 48% had Q fever and 28% had *Bartonella* infection. Q fever endocarditis requires a long course (at least 18 months) of combined therapy using doxycycline (>8 years) and hydroxychloroquine.

### Penicillin allergy

For patients with penicillin allergy, we recommend consulting an infectious diseases physician or clinical microbiologist. For patients with non-anaphylactic allergy, ceftriaxone can usually be substituted for benzylpenicillin in the treatment of streptococcal endocarditis, and cefalothin or cephazolin for di/flucloxacillin when treating staphylococcal infection. For patients with anaphylactic penicillin allergy, vancomycin alone can be used for either streptococcal or staphylococcal infection. Vancomycin plus gentamicin is the only alternative available for enterococcal endocarditis, apart from desensitizing the patient to penicillin.

Teicoplanin is an alternative antibiotic for streptococcal endocarditis, but is not recommended for staphylococcal endocarditis, because the relapse rate is high.

Failure rates with clindamycin and lincomycin are unacceptably high for all types of endocarditis, and it is recommended not to use these antibiotics to treat endocarditis.
Monitoring antibiotic levels when treating endocarditis

Gentamicin
When using low-dose gentamicin (1 mg/kg 8-hourly), we recommend measuring trough levels, maintaining the level <1 mg/L. The aim is to minimize the risk of ototoxicity and nephrotoxicity (see also Appendix 2). For once-daily gentamicin, levels should be monitored using the area-under-the-curve method (see Appendix 2). Older children on long-term gentamicin (>1 week) should ideally be monitored for vestibular and auditory ototoxicity.

Vestibular toxicity can occur even when drug levels are within the normal therapeutic range, and may be irreversible.30 Toxicity may present early during treatment, or weeks after completing therapy. If indicated, baseline audiometry should be performed as soon as possible after starting therapy, and repeated regularly if aminoglycosides are continued >14 days.

Glycopeptides (vancomycin and teicoplanin)
Trough levels of the glycopeptides, vancomycin or teicoplanin, should be monitored to reduce toxicity and ensure adequate levels for killing. For maximal efficacy, the target trough levels are 10–20 mg/L for vancomycin and >20 mg/L for teicoplanin.

Di/flucl/oxa/nafcillin
Monitoring of di/flucl/oxa/nafcillin levels is not indicated with intermittent intravenous dosing. It may be considered in patients receiving flucloxacillin by continuous intravenous infusion.

Monitoring blood parameters when treating endocarditis
It is extremely common for patients on long-term treatment with beta-lactam antibiotics for endocarditis to have delayed adverse events, notably fever, rash, and/or neutropenia, often with eosinophilia. In an 8-year prospective study, 33% of adults treated for endocarditis with beta-lactams developed significant adverse effects.31 Furthermore, 51% of those treated with penicillin G for more than 10 days developed any adverse event and 14% had neutropenia.31 Di/flucl/oxa/nafcillin can also cause fever and neutropenia.31 Flucloxacillin can cause cholestatic hepatitis, though mainly in adults, while dicloxacillin can cause interstitial nephritis.32

We recommend monitoring the differential white cell count for neutropenia and eosinophilia when patients are receiving beta-lactam antibiotics.

Prevention of endocarditis: antibiotic chemoprophylaxis

Question | For children with preexisting heart disease, do prophylactic antibiotics compared with no antibiotics or placebo reduce the risk of endocarditis?

Literature review | We found only one case-control study in adults and children.33

Despite the well-recognized association between recent dental work and endocarditis, it is not absolutely certain that the dental work causes the endocarditis. People who require dental work may already be at higher risk of endocarditis because of their bad teeth. It is known that children develop a transient bacteremia about half of the time when they brush their teeth.34 Thus, it seems logical that dental work might increase the risk of bacteremia and endocarditis in persons with predisposing heart conditions.

It has been recommended for many years to give prophylactic antibiotics to adults and children known to be at increased risk for endocarditis when they have a procedure that is likely to cause bacteremia, such as dental work and some other surgical procedures. The evidence for this practice is extremely weak. A Cochrane systematic review35 found no RCTs, although that is hardly surprising, because it is rare to get endocarditis after a procedure and an RCT would need very large numbers of patients. More surprisingly, the review found only one case-control study,33 which included all the cases of endocarditis in the Netherlands over 2 years. No significant effect of penicillin prophylaxis on the incidence of endocarditis was seen.33

Despite the lack of good evidence, all authorities involved with children and adults at risk for endocarditis continue to recommend antibiotic chemoprophylaxis for certain procedures. The groups known to be at increased risk for endocarditis have been reviewed36 and guidelines have been developed by the American Medical Association.37 These have been modified for children38 and for the Australian Indigenous population (see Table 3.1).39
### Table 3.1 Cardiac conditions and risk for infective endocarditis.

<table>
<thead>
<tr>
<th>High-risk Conditions</th>
<th>Medium-risk Conditions</th>
<th>Low-risk Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prosthetic cardiac valves (including bioprosthetic and homograft)</td>
<td>Congenital cardiac malformations, other than those defined as high or low risk</td>
<td>Surgical repair of atrial septal defect (ASD), ventricular septal defect or patent ductus arteriosus</td>
</tr>
<tr>
<td>Previous infective endocarditis</td>
<td>Hypertrophic cardiomyopathy</td>
<td>Isolated secundum ASD</td>
</tr>
<tr>
<td>Complex cyanotic congenital heart disease (single ventricle, transposition of great arteries, tetralogy of Fallot)</td>
<td>Acquired valvular dysfunction (e.g., rheumatic heart disease) in non-indigenous patients</td>
<td>Previous coronary artery bypass grafts or stents</td>
</tr>
<tr>
<td>Surgically constructed systemic-pulmonary shunts or conduits</td>
<td>Mitral valve prolapse with valvular regurgitation or thickened leaflets</td>
<td>Mitral valve prolapse without regurgitation</td>
</tr>
<tr>
<td>Acquired valvular dysfunction (e.g., rheumatic heart disease) in indigenous patients</td>
<td>Significant valvular/hemodynamic dysfunction associated with septal defects</td>
<td>Previous Kawasaki disease without valve dysfunction</td>
</tr>
<tr>
<td></td>
<td>Severe pulmonary stenosis</td>
<td>Previous rheumatic fever without valve dysfunction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac pacemakers and implanted defibrillators</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild or moderate pulmonary stenosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Physiologic, functional, or innocent heart murmur</td>
</tr>
</tbody>
</table>

Adapted from References 37–39.

Dental procedures for which chemoprophylaxis is recommended, on the basis of the likelihood of causing bacteremia, are dental extractions, periodontal procedures, including scaling, probing, and routine maintenance as well as initial placement of orthodontic bands but not brackets, and prophylactic cleaning of teeth or implants during which bleeding is expected.

The recommendations for non-dental procedures are given in Table 3.2. They are based on likely risk of bacteremia, but there have been no studies to show efficacy.

If it is decided to give antibiotic prophylaxis, it is recommended to give a single dose of antibiotic before the procedure. There is no proven value to giving a follow-up dose 6 hours later, and this is no longer recommended. The recommended regimens are given in Table 3.3.

### 3.2 Acute rheumatic fever

Acute rheumatic fever is an acute inflammatory condition that occurs subsequent to group A streptococcal (GAS) infection. The inflammation can affect joints, skin, central nervous system, and particularly the heart. Rheumatic heart disease is an autoimmune disease in which T-cell damage to the endocardium occurs as a result of mimicry between streptococcal M protein and cardiac myosin. Carditis can occur with the first attack of acute rheumatic fever, or later with recurrences. Lasegue wrote, more than 100 years ago, that rheumatic fever “licks at the joint but bites at the heart.”

Traditional teaching is that the GAS infection is usually of the throat (streptococcal tonsillitis and/or pharyngitis), and this is supported by evidence from a meta-analysis of studies that antibiotic treatment of sore throats reduces the incidence of subsequent
# Cardiac infections

## Table 3.2 Recommendations on procedures and endocarditis prophylaxis.

<table>
<thead>
<tr>
<th>Site</th>
<th>Recommended: High Risk</th>
<th>Not Recommended: Low Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory tract</td>
<td>Tonsillectomy and/or adenoidectomy</td>
<td>Endotracheal intubation</td>
</tr>
<tr>
<td></td>
<td>Surgery involving respiratory mucosa</td>
<td>Flexible bronchoscopy</td>
</tr>
<tr>
<td></td>
<td>Rigid bronchoscopy</td>
<td>Insertion of tympanostomy tubes (grommets)</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Biliary tract surgery</td>
<td>Endoscopy without biopsy</td>
</tr>
<tr>
<td></td>
<td>Esophageal surgery</td>
<td>Transesophageal echocardiography</td>
</tr>
<tr>
<td></td>
<td>Surgery involving intestinal mucosa</td>
<td></td>
</tr>
<tr>
<td>Genitourinary tract</td>
<td>Cystoscopy</td>
<td>Urethral catheterization (if no infection)</td>
</tr>
<tr>
<td></td>
<td>Urethral dilatation</td>
<td>Vaginal procedures</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>Cardiac catheterization</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Balloon angioplasty</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Circumcision</td>
</tr>
</tbody>
</table>

Adapted from Reference 38.

## Table 3.3 Recommendations on antibiotic regimens for endocarditis prophylaxis.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Situation</th>
<th>Antibiotic Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental, oral, respiratory tract, or</td>
<td>Standard general prophylaxis</td>
<td>Amoxicillin 50 mg/kg (max 2 g) orally, 1 hour before procedure</td>
</tr>
<tr>
<td>esophageal procedures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dental, oral, respiratory tract, or</td>
<td>Unable to take medication orally</td>
<td>Ampicillin 50 mg/kg (max 2 g) IV or IM, up to 30 min before procedure</td>
</tr>
<tr>
<td>esophageal procedures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dental, oral, respiratory tract, or</td>
<td>Allergic to penicillin</td>
<td>Clindamycin 20 mg/kg (max 600 mg) orally, 1 hour before procedure (same dose IV up to 30 min before if cannot take orally)</td>
</tr>
<tr>
<td>esophageal procedures</td>
<td></td>
<td>OR</td>
</tr>
<tr>
<td>Gastrointestinal or genitourinary</td>
<td>High risk</td>
<td>Ampicillin 50 mg/kg IV or IM (max 2 g) plus gentamicin 1.5 mg/kg (max 120 mg) IV or IM, up to 30 min before procedure</td>
</tr>
<tr>
<td>tract procedures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal or genitourinary</td>
<td>Moderate risk</td>
<td>Amoxicillin 50 mg/kg (max 2 g) orally, 1 hour before procedure</td>
</tr>
<tr>
<td>tract procedures</td>
<td></td>
<td>OR</td>
</tr>
<tr>
<td>Gastrointestinal or genitourinary</td>
<td>Allergic to ampicillin</td>
<td>Vancomycin 25 mg/kg (max 1 g), infused IV over 1–2 h, finishing up to 30 min before procedure</td>
</tr>
<tr>
<td>tract procedures</td>
<td></td>
<td>If high risk, also give gentamicin 1.5 mg/kg (max 120 mg) IV or IM, up to 30 min before procedure</td>
</tr>
</tbody>
</table>

38
rheumatic fever. Recent data suggest that in Australian Aboriginal children who have a rate of rheumatic fever >300 cases per 100,000 persons per year (among children 5–14 years old) compared to <5 cases per 100,000 persons per year in the non-Aboriginal Australian population, acute rheumatic fever occurs as a result of GAS skin infections (pyoderma or impetigo) and not throat infection. Similar high rates of pyoderma and low rates of sore throat in association with acute rheumatic fever have been reported from Ethiopia, Jamaica, and southern India.

Rheumatic fever is very much a disease of poverty. Another major risk factor is overcrowding, and outbreaks of rheumatic fever have traditionally been reported in boarding schools and army barracks. However, as recently as the 1980s, there was a resurgence of acute rheumatic fever in middle class children in the mid-western USA. This suggests that factors related to the virulence of the organism, the environment, and the host are all important in the etiology of rheumatic fever.

**Diagnosis of acute rheumatic fever**

Rheumatic fever usually presents acutely with fever, evanescent large joint polyarthritis or arthralgia, sometimes with the urticarial rash of erythema marginatum, sometimes with subcutaneous nodules, and sometimes with evidence of acute carditis. Children with Sydenham’s chorea often present much more indolently, with unusual choreiform movements that disappear at night, often involving just one limb, and with a labile affect, but without fever or laboratory evidence of inflammation and often without a history suggesting recent streptococcal infection. Acute rheumatic fever can mimic a number of other conditions, both infective and non-infective, including infective endocarditis, viral infections, juvenile idiopathic arthritis, and Kawasaki disease. In 1944, Duckett Jones published criteria for the diagnosis of acute rheumatic fever, and these have been modified by the American Heart Association. They are useful for decisions about acute treatment and long-term prophylaxis (see below). It can be particularly difficult to decide about the management of children with post-streptococcal arthralgia or arthritis who may or may not be at risk for later carditis. The modified Jones criteria are shown in Table 3.4.

**Table 3.4 Modified Duckett Jones criteria for diagnosing acute rheumatic fever.**

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
<th>Evidence of GAS infection</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute carditis</td>
<td>Arthralgia</td>
<td>Positive culture or rising antibody titer (anti-streptolysin O = ASOT or anti-deoxyribonuclease B = anti-DNase B)</td>
<td></td>
</tr>
<tr>
<td>Polyarthritis</td>
<td>Fever</td>
<td></td>
<td>Need evidence of streptococcal infection plus either two major or one major and two minor criteria (and no other diagnosis)</td>
</tr>
<tr>
<td>Chorea</td>
<td>Elevated ESR or serum C-reactive protein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema marginatum</td>
<td>Prolonged PR interval (first-degree heart block)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sub-cutaneous nodules</td>
<td>Evidence of GAS infection</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Acute rheumatic carditis can affect the endocardium, the myocardium, or the pericardium but usually all three (pancarditis). If there is endocarditis, the mitral valve is most commonly affected, followed by the aortic valve. Valvular insufficiency is usual, but mitral stenosis due to thickening of the valve may develop early in young children. Clinically, children with carditis present with cardiomegaly and heart failure, with tachycardia, with murmurs (e.g., a high-pitched pansystolic murmur radiating to the axilla of mitral incompetence or the Carey Coombs diastolic murmur of mitral stenosis), and rarely with arrhythmias due to myocarditis or with a rub and/or muffled heart sounds due to pericarditis.

**Prevention of acute rheumatic fever**

**Antibiotic treatment of sore throat**

A Cochrane review of the treatment of acute sore throat found that antibiotics reduced acute rheumatic fever by more than three quarters (RR 0.22, 95% CI 0.02–2.08). Prompt treatment of streptococcal sore throat is important, but not all children who develop rheumatic fever have an identifiable sore throat, and some may have skin sepsis instead.

**Treatment of skin sepsis**

Although it has not been proven that reducing skin sepsis in Aboriginal children prevents acute rheumatic
Cardiac infections

fever, it has been shown that the incidence of impetigo and pyoderma can be reduced by using permethrin to treat scabies.51 Pyoderma was also reduced, but only temporarily, when Aboriginal children were given a single dose of azithromycin in a trachoma program.52

Treatment of acute rheumatic fever

Children with evidence of active infection should be treated with antibiotics to eradicate group A streptococcus (see p. 178).

The mainstay of anti-inflammatory treatment of acute rheumatic fever has been the use of aspirin, and it has been reported that the rapid defervescence of fever soon after starting aspirin is virtually diagnostic.53 A Cochrane review of different anti-inflammatory drugs in acute rheumatic fever, however, found no RCTs comparing aspirin with placebo, so this observation is anecdotal.54

The Cochrane review included eight RCTs involving 996 people, and comparing different steroids (ACTH, cortisone, hydrocortisone, dexamethasone, and prednisone) and intravenous immunoglobulin with aspirin, placebo, or no treatment.54 Six of the trials were conducted between 1950 and 1965. Overall there was no significant difference in the risk of cardiac disease at 1 year between the corticosteroid-treated and aspirin-treated groups (RR 0.87, 95% CI 0.66–1.15). Similarly, use of prednisone (RR 1.78, 95% CI 0.98–3.34) or intravenous immunoglobulins (RR 0.87, 95% CI 0.55–1.39) did not reduce the risk of developing heart valve lesions at 1 year compared to placebo.54

The optimal management of inflammation in acute rheumatic fever remains uncertain. In one study, naproxen was found to be as effective as aspirin, and substantially less likely to be associated with elevated liver enzymes.55 The role of corticosteroids remains unclear.

Antibiotic prophylaxis of rheumatic fever

Question | For patients with a history of rheumatic fever do long-term prophylactic antibiotics, compared with no antibiotics or placebo, reduce the incidence of recurrent attacks of rheumatic fever and/or exacerbation of existing rheumatic heart disease, or the development of new rheumatic heart disease?

Literature review | We found 10 studies on penicillin prophylaxis with highly variable design, and 2 meta-analyses,56,57 including a Cochrane review.56

The Cochrane review56 did not pool the 9 studies found, because of heterogeneity and different study design. Three trials, with 1301 patients, compared penicillin to placebo. Only 1 of these 3 studies found that penicillin reduced rheumatic fever recurrence (RR 0.45, 95% CI 0.22–0.92) and streptococcal throat infection (RR 0.84, 95% CI 0.72–0.97). Four trials (n = 1098) compared long-acting IM penicillin with oral penicillin: all showed that IM penicillin reduced rheumatic fever recurrence and streptococcal throat infections compared to oral penicillin. It is not clear whether this is because of better compliance or because better antibiotic levels can be achieved with long-acting IM penicillin. One trial (n = 360) comparing 2-weekly with 4-weekly IM penicillin found 2-weekly was better at reducing rheumatic fever recurrence (RR 0.52, 95% CI 0.33–0.83) and streptococcal throat infections (RR 0.60, 95% CI 0.42–0.85). One trial (n = 249) showed 3-weekly IM penicillin reduced streptococcal throat infections (RR 0.67, 95% CI 0.48–0.92) compared to 4-weekly IM penicillin.56

The Cochrane review authors concluded that IM penicillin seemed to be more effective than oral penicillin in preventing rheumatic fever recurrence and streptococcal throat infections, and that 2-weekly or 3-weekly IM injections appeared to be more effective than 4-weekly injections.56 However, they state that the evidence is based on poor-quality trials.

A more recent meta-analysis included 10 trials (n = 7665) and agreed that, in general, the methodologic quality of the studies was poor.57 All the included trials were conducted during the period 1950–1961, and in 8 of the trials the study population was young adult males living on United States military bases. The meta-analysis revealed an overall protective effect for the use of antibiotics against acute rheumatic fever of 68% (RR 0.32, 95% CI = 0.21–0.48). When meta-analysis was restricted to trials evaluating penicillin, the protective effect was 80% (RR 0.20, 95% CI = 0.11–0.36). They concluded that 60 children with rheumatic fever needed to be treated with prophylactic penicillin to prevent one case of rheumatic carditis (number needed to treat, NNT = 60).57
prove delivery. Particularly from New Zealand, that these registers improve delivery. There is observational evidence, particularly from New Zealand, that these registers improve delivery.59

We recommend continuous antimicrobial prophylaxis against *S. pyogenes* infection for patients with a well-documented history of rheumatic fever. IM administration of long-acting penicillin is preferred, especially in remote areas, as it is more effective and usually leads to better adherence: We prefer 3-weekly injections, but will give 4-weekly if it improves compliance. We recommend that treatment be given in a convenient site, such as a health center or in the patient’s home.

Because compliance is so important and IM penicillin so painful, the rheumatic fever service in the Northern Territory of Australia mixes each 2 mL IM injection of benzathine penicillin with 0.5 mL of lignocaine (J. Carapetis, personal communication, 2006). Although we can find no evidence regarding safety and efficacy of this practice, we recommend using this regimen if compliance is likely to depend on it.

We recommend:

- **Benzathine penicillin:** adult and child $\geq 20$ kg: 900 mg (=1.5 million units); child $< 20$ kg: 450 mg (=750,000 units) IM, every 3 or 4 weeks

If IM penicillin absolutely cannot be given, usually due to adherence problems, we recommend:

- **Phenoxymethyl penicillin (all ages)** 250 mg orally, 12-hourly

For patients with anaphylactic penicillin allergy, we recommend:

- Erythromycin 250 mg orally, 12-hourly OR erythromycin ethyl succinate 400 mg orally, 12-hourly (all ages)

The duration of prophylaxis is given in Table 3.5.

### Table 3.5 Duration of prophylaxis for rheumatic fever.68

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommended Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatic fever with no carditis</td>
<td>For 5 years, or until 21 years old, whichever is longer</td>
</tr>
<tr>
<td>Rheumatic fever with carditis, but with no residual valve disease</td>
<td>For 10 years or well into adulthood, whichever is longer</td>
</tr>
<tr>
<td>Rheumatic fever with carditis, with residual valve disease</td>
<td>For at least 10 years after last episode, and until at least 40 years old, but sometimes lifelong</td>
</tr>
</tbody>
</table>

The WHO has recommended that registers be set up to monitor compliance in areas with a high prevalence of rheumatic fever.58 There is observational evidence, particularly from New Zealand, that these registers improve delivery.59

We recommend continuous antimicrobial prophylaxis against *S. pyogenes* infection for patients with a well-documented history of rheumatic fever. IM administration of long-acting penicillin is preferred, especially in remote areas, as it is more effective and usually leads to better adherence: We prefer 3-weekly injections, but will give 4-weekly if it improves compliance. We recommend that treatment be given in a convenient site, such as a health center or in the patient’s home.

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We recommend:

- **Benzathine penicillin:** adult and child $\geq 20$ kg: 900 mg (=1.5 million units); child $< 20$ kg: 450 mg (=750,000 units) IM, every 3 or 4 weeks

If IM penicillin absolutely cannot be given, usually due to adherence problems, we recommend:

- **Phenoxymethyl penicillin (all ages)** 250 mg orally, 12-hourly

For patients with anaphylactic penicillin allergy, we recommend:

- Erythromycin 250 mg orally, 12-hourly OR erythromycin ethyl succinate 400 mg orally, 12-hourly (all ages)

The duration of prophylaxis is given in Table 3.5.

### References


CHAPTER 4
Cervical infections

4.1 Cervical lymphadenopathy

Children often have palpable, and sometimes visible, lymph nodes. In a study of over 3500 healthy 8–9-year-old Swedish schoolchildren, 27.6% had palpable submandibular, cervical, and/or supraclavicular lymph nodes.1 The most common location was submandibular. In 8.7% of children, the lymph nodes were 5 mm or greater in diameter. Boys had a significantly higher prevalence of palpable lymph nodes than girls. There was also seasonal variation. Children who had positive skin-prick testing to atypical mycobacteria (Mycobacterium avium or Mycobacterium scrofulaceum) did not have a higher prevalence of palpable lymph nodes than those not infected.1

What is pathological? The term cervical lymphadenopathy is often reserved for lymph nodes > 1 cm in diameter,2–4 although a cutoff of 1.5 cm or greater has been used for Kawasaki disease,5 while cutoffs from 1 to 2.5 cm have been used to define enlarged lymph nodes in different studies. Clearly, the reported incidence of lymphadenopathy will vary according to the definition.

Children with small lymph nodes who are otherwise well do not need any investigation. Their lymph nodes are thought to be minimally enlarged in response to common viral respiratory infections, which are the commonest cause of minor cervical lymphadenopathy in young children.2–4

Causes of cervical lymphadenopathy

The causes of cervical lymphadenopathy are myriad. Their frequency depends on various factors, the most important of which are the child’s age and whether the child is from a rich, industrialized country with a temperate climate or from a poor, tropical country. In the former situation, most studies have found that Staphylococcus aureus is the most common cause of cervical lymphadenitis, particularly in infancy, followed by group A streptococcus and atypical mycobacteria.6–12 In the latter, impoverished situation, M. tuberculosis, and HIV infection are now among the most important causes of lymphadenopathy, although pyogenic infection is also extremely common.13–15

S. aureus probably reaches the lymph nodes through the skin, although there may be no obvious abrasion. Other organisms, such as group A streptococcus, drain to the regional lymph nodes from the nasopharynx. M. tuberculosis, and less common causes of lymphadenitis, such as Streptococcus pneumoniae16 and group B streptococcus, may spread via the bloodstream or locally from the nasopharynx.17

Table 4.1 summarizes some of the more important of the myriad causes of cervical lymphadenopathy, as reported in the literature.1–15 We have deliberately excluded some of the rarer causes, which may be found in review articles.4 A long list of the causes is not very helpful, so we have combined the underlying pathology with the usual clinical presentation.

Cervical lymphadenopathy: the history

Acute or chronic presentation

There is an important distinction between children who present with acute neck swelling, which is often tender and associated with fever, and children who present with a more gradual onset of non-tender swelling in the neck, often without fever. The former presentation is suggestive of an acute suppurative process, as with bacterial adenitis (including cat scratch), or suggestive of Kawasaki disease (see Section 6.9, p. 63). In contrast, children with lymphadenitis due to mycobacterial infection, either M. tuberculosis or atypical mycobacteria, tend to present in a far more indolent way. Although children with TB lymphadenitis may have systemic symptoms of fever, night sweats, and weight loss, it is far more common for them to be afebrile and well, and present just with enlarging or discharging neck glands.13,14
Table 4.1  Some of the more common causes of cervical lymphadenopathy in children.

<table>
<thead>
<tr>
<th>Underlying Pathology</th>
<th>Usual Clinical Presentation</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute bacterial suppurative lymphadenitis</td>
<td>Fever, tenderness, red, inflamed</td>
<td><em>Staphylococcus aureus</em>  &lt;br&gt; <em>Group A streptococcus</em>  &lt;br&gt; Cat scratch (<em>Bartonella henselae</em>)  &lt;br&gt; Anaerobes</td>
</tr>
<tr>
<td>Chronic bacterial lymphadenitis</td>
<td>Fever may or may not be present, non-tender, reddish-purple skin discoloration, may suppurate</td>
<td><em>Mycobacterium tuberculosis</em>  &lt;br&gt; Atypical mycobacteria</td>
</tr>
<tr>
<td>Acute viral</td>
<td>Fever, tenderness, may have palatal petechiae, eyelid edema, splenomegaly</td>
<td>EBV</td>
</tr>
<tr>
<td>Chronic viral</td>
<td>Other features of HIV infection</td>
<td>HIV</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Fever, tenderness, nodes usually unilateral and may resemble cervical abscess</td>
<td>Kawasaki disease</td>
</tr>
<tr>
<td>Protozoal</td>
<td>Asymptomatic or chronic illness with weakness and debility</td>
<td><em>Toxoplasma gondii</em> (NB: CMV and EBV can present this way)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Fever, night sweats, weight loss</td>
<td>Lymphoma</td>
</tr>
</tbody>
</table>

Toxoplasmosis also tends to present indolently in older children and adolescents, with isolated cervical or occipital lymphadenopathy. The lymph nodes are not tender, do not suppurate, are usually discrete, and stay enlarged for less than 4–6 weeks. A form of the disease characterized by chronic lymphadenopathy has been described, and lymph-node enlargement can fluctuate for months, associated with weakness and debility.

Malignancy is a relatively rare cause of cervical lymphadenopathy, usually in older children.

Unilateral or bilateral lymphadenopathy

- Bilateral cervical lymphadenitis is most commonly seen with group A streptococcal infection and with viral infections, such as EBV.
- Cat scratch disease is almost always unilateral, and Kawasaki disease usually unilateral.
- Mycobacterial infections can be unilateral or bilateral.

Site of neck swelling

The site of lymph node swelling can be helpful:

- Post-erior cervical lymphadenopathy (occipital nodes) occurs acutely with rubella and EBV infection, and chronically with malignancy.
- Cat scratch usually causes preauricular or sub-mandibular swelling.
- Malignancy is more likely to affect supraclavicular nodes (or post-erior nodes) than anterior nodes.
- Acute bilateral parotid swelling (the parotid overlies the mandible) suggests mumps.
- Chronic bilateral parotid swelling may be due to HIV infection or Sjögren disease.
- Acute, unilateral parotid swelling, particularly if recurrent, suggests recurrent parotitis of childhood.

History of cat contact

A history of exposure to cats, and particularly to kittens or a sick cat, can help suggest a diagnosis of cat scratch disease (see also Section 6.10, p. 66). There may be a nodule at the site of a previous scratch, which is likely to be on the face to cause cervical lymphadenopathy (scratches on the hand give rise to epitrochlear or axillary lymphadenopathy and on the leg give rise to inguinal lymphadenopathy). On the other hand, *B. henselae* can be transmitted by a lick from a cat, so a history of close contact alone is sufficient to raise suspicion of the diagnosis in a child with fever and cervical lymphadenopathy. In addition, children with cat scratch lymphadenopathy may have a granulomatous
conjunctivitis (Parinaud oculoglandular syndrome) with granulomata visible on the palpebral conjunctiva.

Toxoplasma infection has also been associated with cat contact as well as with eating undercooked meat.16

History of exposure to infection
It is obviously important to ask about exposure to possible infections, such as TB, group A streptococcal infection, and viral infections. Some families will hide a family history of TB because of the stigma.

Dental infections
· Dental abscess and periodontal infection can be associated with acute lymphadenitis due to anaerobes.7,9
· Dental infection may result in Ludwig angina, a brawny induration of the floor of the mouth and suprathyroid region (bilaterally), presenting acutely with fever, neck swelling, bilateral submandibular swelling, or midline swelling under the jaw and elevation of the tongue22 (see Section 4.5, p. 36).
· Actinomycosis is a chronic infection that can result from chronic dental and/or jaw infection and presents with chronic, unilateral, brawny sub-mandibular swelling23 (see Section 4.2, p. 35).

Age
The age of the child often gives a clue to the likely cause of lymphadenopathy.1–19 As stated above, the etiology is likely to be different if the child presents with acute, tender enlargement of the cervical nodes with overlying redness (see Table 4.2) or with subacute, non-tender neck swelling (see Table 4.3).

Neonates and young infants
Neonates and young infants can present with facial cellulitis and cervical adenitis due to group B streptococcal infection.17 In one small study, the mean age of babies with group B streptococcal infection was 5 weeks, infected babies were more likely to be boys presenting with poor feeding and irritability, and sometimes ipsilateral otitis media, as well as with facial or submandibular cellulitis.17 Most babies were bacteremic.17

Table 4.2 Age and likely diagnosis for acutely inflamed, tender lymphadenopathy.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Most Common Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate (&lt;1 month)</td>
<td>Staphylococcus aureus</td>
</tr>
<tr>
<td></td>
<td>Group B streptococcus</td>
</tr>
<tr>
<td>Infant (1 month –</td>
<td>Staphylococcus aureus</td>
</tr>
<tr>
<td>1 year)</td>
<td>Group A streptococcus</td>
</tr>
<tr>
<td></td>
<td>Adenovirus or HSV infection</td>
</tr>
<tr>
<td></td>
<td>Kawasaki disease</td>
</tr>
<tr>
<td>Young child (1–4</td>
<td>Staphylococcus aureus</td>
</tr>
<tr>
<td>years)</td>
<td>Group A streptococcus</td>
</tr>
<tr>
<td></td>
<td>Adenovirus, HSV, or EBV infection</td>
</tr>
<tr>
<td></td>
<td>Kawasaki disease</td>
</tr>
<tr>
<td></td>
<td>Cat scratch disease</td>
</tr>
<tr>
<td>Older child (&gt; 4</td>
<td>Cat scratch disease</td>
</tr>
<tr>
<td>years)</td>
<td>EBV infection</td>
</tr>
<tr>
<td></td>
<td>Anaerobic bacteria (periodontal disease)</td>
</tr>
</tbody>
</table>

systemic lupus erythematosus and drug-induced lymphadenopathy (e.g., phenytoin, isoniazid) may need to be considered,4 as well as the diagnoses in Tables 4.2 and 4.3.

Examination of child with cervical lymphadenitis
The general physical examination is important to look for signs of malnutrition or poor growth that would raise the possibility of TB, HIV infection, immunocompromise, or malignancy.

The color of the overlying skin may help. Erythema and warmth suggests a pyogenic process or Kawasaki

Table 4.3 Age and likely diagnosis for sub-acute, non-tender neck swelling.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Most Common Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate (&lt;1 month)</td>
<td>Congenital lesion (branchial cleft cyst, cystic hygroma)</td>
</tr>
<tr>
<td>Infant (1 month –</td>
<td>Congenital lesion</td>
</tr>
<tr>
<td>1 year)</td>
<td>TB (in endemic region)</td>
</tr>
<tr>
<td>Older child (&gt; 4 years)</td>
<td>Toxoplasmosis</td>
</tr>
<tr>
<td></td>
<td>TB</td>
</tr>
<tr>
<td></td>
<td>Malignancy</td>
</tr>
</tbody>
</table>
disease. The skin overlying atypical mycobacterial infection often has a purplish discoloration, but it may look identical in TB lymphadenitis.

The character of the lymph nodes is important (see Table 4.1). Fluclavance suggests pus formation and the need for drainage by needle aspiration or surgical intervention. Malignant nodes are usually hard and often fixed to underlying tissues.

**Investigation of cervical lymphadenitis**

**Hematology**

Laboratory parameters may be diagnostically useful in infectious mononucleosis (showing atypical lymphocytes), or in malignancy (blast cells, pancytopenia), and helpful in suspected Kawasaki disease (neutrophilia, etc.; see Section 6.9, p. 63).

**Fine needle aspiration**

Fine needle aspiration (FNA) can be used to diagnose both pyogenic infections and mycobacterial infections (see p. 33). Needle aspiration is therapeutically useful for draining small abscesses, and can avoid the need for surgery.

In an observational study from Kentucky of 119 children undergoing FNA, 5 aspirates revealed malignancy and 8 grew a microorganism. The remaining children were diagnosed as having a benign process, most commonly reactive lymphadenitis. The accuracy was 98%, and the procedure usually obviated the need for an excisional biopsy.

**Investigations for suspected mycobacterial infection**

**Tuberculin skin testing**

In a situation of endemic TB, a simple clinical algorithm that identified children with persistent (>4 weeks) cervical lymphadenopathy, no visible local cause such as superficial pyoderma, no response to antibiotics against pyogenic organisms, and a cervical mass 2 cm in diameter or greater identified over 98% of cases, without the need for tuberculin skin testing.

For children with suspected tuberculous or atypical mycobacterial infection, in an industrialized country where TB is relatively uncommon, skin-prick testing can be extremely helpful. If a child with cervical lymphadenitis has a negative tuberculin skin test (TST) with human purified protein derivative (PPD), this virtually excludes TB. The only exceptions would be a child who is extremely unwell, in which case TSTs can be negative due to anergy, or if the test is not performed adequately.

Some countries have skin tests for atypical mycobacterial infection, using avian PPD or sensinet (purified from *M. avium* or *M. scrofulaceum* PPD or sensinet (from *M. scrofulaceum*). In one study, 59 children with culture-proven non-tuberculous mycobacterial infection also had differential skin testing performed with avian and human PPD. A positive response to avian PPD (>10 mm) correctly identified 58 of 59 infected children (98.3%).

There is cross-reaction between avian and human responses, and so children with a positive avian skin test often have positive TSTs using human PPD. In children with proven avian disease, the avian response is almost always greater than the human response: it was at least 2 mm greater in 55 cases (93%) in the study shown in Figure 4.1. Ten children (17%) with atypical mycobacterial infection had a negative human Mantoux. No patient had both a negative human and avian Mantoux. Thus, if avian or scrofulaceum PPD is not available, a positive human Mantoux is helpful, but could be due to cross-reaction or true human TB, while

![Figure 4.1 TST responses (Mantoux tests) to avian and human PPD in children with proven non-tuberculous mycobacterial infection (line of identity drawn). (Reprinted with permission from Reference 26.)](image-url)
a negative human Mantoux does not exclude atypical mycobacterial infection but makes it less likely.

**Fine needle aspiration for mycobacterial infection**
Definitive diagnosis of mycobacterial infections, both human and atypical, can be made using material obtained either by surgical excision or by fine needle aspiration (FNA). While it is often quoted that the definitive treatment of atypical mycobacterial infection is total excision of infected nodes, there are no RCTs of the treatment of atypical mycobacterial infection comparing total excision with needle aspiration alone or with needle aspiration plus antimicrobials. The extremes of outcome of atypical mycobacterial infection are spontaneous resolution and chronic, discharging sinuses. We currently recommend referring all children with suspected mycobacterial lymphadenitis to an experienced pediatric surgeon (see Definitive surgery, below).

**Polymerase chain reaction (PCR)**

**Question** | In children with suspected mycobacterial lymphadenitis, is PCR a sensitive and specific test for diagnosing and excluding infection?

**Literature review** | We found 10 studies comparing PCR with culture, histopathology or ELISA. PCR has been used on lymph node aspirates to diagnose mycobacterial infections. The sensitivity of PCR for detecting TB in high-risk populations varied from 55% on FNAs and 68% on biopsy specimens to up to 96% on excised nodes. PCR was found to be at least as sensitive as existing techniques of Ziehl–Neelsen stain and histopathology, but did not alter treatment in a high-risk setting. False-positive tests were sometimes a problem, with the specificity reported from 38 to 86%.

One advantage of PCR is that if a positive result is obtained, the product can be sequenced to distinguish between *M. tuberculosis* and atypical mycobacteria. This is important because culture takes weeks, and is particularly useful in a developed country setting, where both *M. tuberculosis* and atypical mycobacterial infection are seen and are difficult to distinguish clinically. Another advantage, is that when there is widespread resistance to antituberculous drugs, PCR techniques can be used to look for mutations predicting resistance.

**Treatment of cervical lymphadenopathy**

**Fine needle aspiration**
The potential therapeutic role of FNA, in addition to its diagnostic role, for pyogenic and mycobacterial infections, has been discussed in sections above.

**Definitive surgery**
Surgical excision may be necessary to obtain an adequate diagnostic specimen and for therapeutic reasons in managing large abscesses and mycobacterial infections.

**Antibiotics for pyogenic infections**
Obviously it is best to base antibiotic treatment on microbiologic information from gram stain or culture. Where this is not possible, antibiotic therapy is based on the likely organisms, staphylococci and streptococci.

If oral therapy is possible, we recommend:

- **cephalexin 25 mg/kg (max 1 g) orally, 6-hourly** OR
- **di/fluco/naflcin 25 mg/kg (max 1 g) orally, 6-hourly** OR
- **clindamycin 10 mg/kg (max 400 mg) orally, 8-hourly**

Clindamycin is recommended if, because of ethnicity or local epidemiology, there is a high likelihood of community-acquired MRSA infection.

For more severe infections, we recommend:

- **di/fluco/naflcin 50 mg/kg (max 2 g) IV, 6-hourly** OR
- **cefazolin 25 mg/kg (max 1 g) IV, 6-hourly OR**
- **clindamycin 10 mg/kg (max 400 mg) IV, 8-hourly**

We recommend clindamycin or the combination of penicillin and metronidazole for dental-associated infections, because of the likelihood of anaerobic infection.

**Treatment for tuberculous cervical lymphadenitis**
The treatment of childhood cervical TB is with antituberculous drugs. A systematic review concluded that short-course therapy (6 months) has a low relapse rate, and is as effective as prolonged therapy.
**Daily regimen**

For the daily regimen, we recommend:

- isoniazid 10 mg/kg (max 300 mg) orally, daily for 6 months **PLUS**
- rifampicin 10 mg/kg (max 600 mg) orally, daily for 6 months **PLUS**
- pyrazinamide 25 mg/kg (max 2 g) orally, daily for 2 months

Because of concerns about its effect on vision, ethambutol is not recommended for children <6 years old. If used for older children instead of or as well as pyrazinamide, the dose is 15 mg/kg daily for 2 months, but we recommend stopping earlier if the organism is shown to be sensitive to isoniazid and rifampicin.

**Three-times-weekly regimen (with directly observed therapy)**

For the three-times-weekly regimen, we recommend:

- isoniazid 15 mg/kg (max 600 mg) orally, three times weekly for 6 months **PLUS**
- rifampicin 15 mg/kg (max 600 mg) orally, three times weekly for 6 months **PLUS**
- pyrazinamide 50 mg/kg (max 3 g) orally, three times weekly for 2 months

Because of concerns about its effect on vision, ethambutol is not recommended for children <6 years old. If used for older children instead of or as well as pyrazinamide, the dose is 30 mg/kg three-times weekly for 2 months, but we recommend stopping earlier if the organism is sensitive to isoniazid and rifampicin.

Children’s enlarged lymph nodes may shrink and disappear on antituberculous drugs initially, but enlarge again while still on therapy. If therapy is directly observed, by far the most likely explanation is paradoxical enlargement due to an immune reaction to TB proteins, which typically occurs about 2 months into therapy.**42**

**Treatment for atypical mycobacterial infections**

Surgical excision of infected nodes is usually curative.**43** Most experts advocate early excisional biopsy to maximize the ability to recover the causative organism; to prevent further cosmetic damage; to remove infected tissue before more extensive spread occurs, making later surgery more difficult; and to cure the disease.**43** Surgery can be difficult, but complications, particularly facial nerve damage, are uncommon when the procedure is performed by an experienced surgeon. Most surgeons use dissection and/or curettage to remove infected tissue. In one study, 8 of 11 patients who initially underwent an incisional biopsy or incision and drainage developed a recurrence or draining sinus tract requiring a second surgical procedure, compared with only 1 of 15 patients who initially underwent a complete excision.**44** Recurrences can occur usually within 3 months of the initial surgery, but sometimes many months later, even when seemingly curative surgery has been performed.**45,46** This is usually due to leaving a deep collection behind, sometimes called a collar-stud abscess, which can break through to the surface later.

Newer antituberculous drugs, notably clarithromycin and azithromycin, have some activity against atypical mycobacteria. There have been no RCTs comparing surgery with medical therapy.**46** A retrospective study reviewed 19 patients with presumed or proven atypical mycobacterial lymphadenitis: 9 were cured by immediate surgical excision, whereas 10 were treated initially with macrolide-containing chemotherapy. Of these 10 patients, 5 were cured with chemotherapy alone and 5 required subsequent surgical excision.**47** Thus, drug regimens effective against atypical mycobacteria can be tried if surgery is contraindicated. There are no data on whether it is better to use azithromycin or clarithromycin alone or two or three drugs, but data on respiratory infections with atypical mycobacteria favor the use of two or three drugs (see p. 202)

**Treatment of lymphadenitis due to cat scratch disease**

Cat scratch disease (B. henselae infection) is self-limiting in immunocompetent patients, and most cases do not require antibiotic therapy (see Section 6.10, p. 66). Antibiotic treatment, with azithromycin, is recommended for immunocompetent patients with lymphadenopathy which has not resolved after a month, or when the lymphadenopathy is associated with significant morbidity.**48**

For treatment of cat scratch disease, we recommend:

- azithromycin 10 mg/kg (max 500 mg) orally, on day 1, then 5 mg/kg (max 250 mg) orally, daily for 4 more days
4.2 Cervicofacial actinomycosis

Actinomycosis is a chronic, granulomatous infection caused by Actinomyces species. These are filamentous, branching, slow-growing, gram-positive anaerobic bacilli found as commensals in the human oropharynx and gastro-intestinal tract. Actinomycoses do not invade normal tissues and require trauma to the mucous surface to cause disease. Cervicofacial actinomycosis is the most common form and usually arises from the teeth or mandible. It is rare in children and we could find only case reports and one small case series. It causes a perimandibular abscess with a characteristic woody feel, due to fibrosis. There may be sinus discharge of yellow sulfur granules. The diagnosis is mainly clinical, usually but not always backed up by microbiologic confirmation. In children, actinomycosis can rarely cause chronic osteomyelitis of the mandible.

Infection is indolent, and classic teaching is that therapy is with high-dose intravenous penicillin for 2–6 weeks, followed by oral penicillin or amoxicillin for a period of 6–12 months. A recent paper described 2 adults whose cervical actinomycosis responded to much shorter courses of IV and oral penicillin. The authors review the literature, which shows weak, observational evidence for prolonged courses. They argue that treatment should be individualized and each patient’s response monitored. We agree with this approach, and recommend:

benzylpenicillin 30 mg (50,000 U)/kg (max 1.2 g or 2 million U) IV, 4-hourly for 1–2 weeks THEN
amoxicillin 15 mg/kg (max 500 mg) orally, 8-hourly until resolved

4.3 Nocardiosis

Both immunocompetent and immunocompromised patients can rarely develop lymphocutaneous infection due to the opportunist saprophytic soil organism, Nocardia. An initial traumatic lesion on the face develops over 1–2 weeks into a popular lesion, with fever and a unilateral enlarged, tender submaxillary gland. Prolonged therapy with cotrimoxazole or a sulfonamide is recommended (6–12 weeks for immunocompetent and 6–12 months for immunocompromised children).

4.4 Deep neck infections

Deep neck or deep cervical fascial space infections generally result from contiguous spread from the respiratory tract or periodontal region, although hematogenous spread may occur. These infections are rare, but potentially life-threatening. The major deep neck infections are peritonsillar abscess (or quinsy), retropharyngeal abscess, and lateral pharyngeal abscess; some refer to these generically as parapharyngeal abscesses.

The characteristic features are shown in Table 4.4.

There are some general management points that apply to all three:
- All can cause acute airway obstruction, which may require immediate airway management.
- Frank pus generally forms on about the fifth day of infection.
- If antibiotic treatment is started early, generally within the first 24–48 hours following the onset of pain when the infection is at the stage of cellulitis, the condition may resolve by fibrosis without abscess formation and without the need for surgery.

<table>
<thead>
<tr>
<th>Infection</th>
<th>Location</th>
<th>Peak Age</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peritonsillar abscess</td>
<td>Tonsillar capsule</td>
<td>&gt; 5 years</td>
<td>Unilateral swelling around tonsil, displacement of uvula; trismus</td>
</tr>
<tr>
<td>Retropharyngeal abscess</td>
<td>Between post-erior pharynx and prevertebral fascia</td>
<td>&lt; 4 years</td>
<td>Neck pain, limited neck extension, torticollis. Variable: stridor, drooling, respiratory distress, visible post-erior pharyngeal bulging</td>
</tr>
<tr>
<td>Lateral pharyngeal abscess</td>
<td>Anterior and post-erior pharyngomaxillary space</td>
<td>&gt; 8 years</td>
<td>Trismus, swelling in the parotid area, or tonsillar fossa</td>
</tr>
</tbody>
</table>
**Peritonsillar abscess (quinsy)**

Peritonsillar abscess is a complication of tonsillopharyngitis. The organisms responsible are predominantly aerobic streptococci, including group A streptococcus, and anaerobes. The diagnosis is usually apparent clinically, although trismus may make it difficult to look in the mouth.

Although there have been anecdotal reports of cure with medical treatment alone, there is consensus that surgery is necessary. Initial studies concluded that immediate tonsillectomy was superior in terms of duration of illness to immediate surgical drainage and delayed (interval) tonsillectomy. Subsequently, studies compared needle drainage with incision and drainage. Results were conflicting, with some finding needle aspiration to be highly effective and others finding that abscesses often recurs following needle aspiration. A meta-analysis found five RCTs on surgical technique, which indicated that needle aspiration, incision and drainage, and quinsy tonsillectomy are all effective for initial management, but could not say that any one was superior.

For antibiotic therapy, we recommend:

- benzylpenicillin 30 mg/kg (max 1.2 g) IV, 6-hourly PLUS
- metronidazole 7.5 mg/kg (max 500 mg) IV, 12-hourly

or alternatively, on its own:

- clindamycin 10 mg/kg (max 450 mg) IV, 8-hourly

Once improving, treatment can be continued with oral amoxicillin-clavulanate or clindamycin.

**Retropharyngeal abscess**

Retropharyngeal abscess follows infection of the nasopharynx, paranasal sinuses, or middle ear, and trauma can predispose. It can occur as early as the neonatal period, but the peak incidence is about 3 years. Some reports emphasize that children often present with respiratory obstruction and stridor, some that the presentation can mimic epiglottitis while others find that stridor and respiratory distress are rare. The clinical presentation is age-dependent. Older children are more likely to complain of neck pain, sore throat, and difficulty swallowing, while younger children are more likely to have stridor, refusal to swallow, dysphonia, drooling, and neck extension.

Plain neck radiographs show widening of the prevertebral space in many patients, as many as 83% in one study. CT scan with contrast has been reported as 81–100% accurate in some studies, but other studies which compared CT with operative findings found a far lower sensitivity of 43–61%. Many children can be managed medically without the need for surgical drainage. Some authorities advocate CT-guided drainage, but there are no RCTs comparing medical and surgical management. Retropharyngeal abscesses are usually polymicrobial, with anaerobes, streptococci, *S. aureus*, and Gram-negative bacilli all common.

We recommend:

- clindamycin 10 mg/kg (max 450 mg) IV, 8-hourly PLUS
- gentamicin <10 years: 7.5 mg/kg; ≥10 years: 6 mg/kg IV, daily

or alternatively,

- cefotaxime 25 mg/kg (max 1 g) IV, 8-hourly PLUS
- metronidazole 7.5 mg/kg (max 500 mg) IV, 12-hourly

**Lateral pharyngeal abscess**

The organisms causing lateral pharyngeal abscess are mouth flora, as for peritonsillar abscess. The same strictures apply with regard to diagnosis, early antibiotic treatment using the same antibiotics as for peritonsillar abscess above, and the need for drainage if there is frank pus and/or failure to respond to medical treatment.

**4.5 Ludwig angina**

Ludwig angina is a rapidly progressive cellulitis and edema of the soft tissues of the neck and floor of the mouth, which results in swelling of the anterior neck below the lower jaw and swelling and elevation of the tongue. It originates in the region of the submandibular gland, and is usually odontogenic. Many adult patients with Ludwig angina are debilitated due to chronic diseases like diabetes, alcoholism or HIV infection. In contrast, affected children are often otherwise healthy.
Early signs and symptoms of obstruction may be subtle. Early recognition of the disease and appropriate airway management is vital, because airway compromise is the leading cause of death.59

For immediate, empiric antibiotic treatment, because infection is usually odontogenic, we recommend:

- **Benzylpenicillin**: 30 mg/kg (max 1.2 g) IV, 6-hourly (PLUS)
- **Metronidazole**: 7.5 mg/kg (max 500 mg) IV, 12-hourly

or alternatively, use on its own:

- **Clindamycin**: 10 mg/kg (max 450 mg) IV, 8-hourly

### 4.6 Lemierre syndrome

Lemierre syndrome is a rare, aggressive, oropharyngeal infection consisting of pharyngitis, bacteremia, and supplicative thrombophlebitis of the internal jugular vein, often complicated by metastatic septic emboli. The most common cause is *Fusobacterium necrophorum*, a Gram-negative, non-spore-forming, obligate anaerobe, which is part of the normal oral flora. Other organisms, mainly anaerobes, may be isolated alone or with *Fusobacterium* from children with Lemierre syndrome.71–73

The septic emboli may cause pulmonary involvement with cavitating pneumonia, empyema, and lung abscess, although in one review, the most common finding on chest X-ray at presentation was pulmonary infiltrates in the absence of cavitation. The second most common site of septic embolization is the joints, with the hip, shoulders, and knees most frequently involved. Hepatic or splenic abscesses can occur rarely.71–73

The management is with antibiotics. The use of heparin is controversial. We recommend:

- **Benzylpenicillin**: 30 mg/kg (max 1.2 g) IV, 6-hourly (PLUS)
- **Metronidazole**: 7.5 mg/kg (max 500 mg) IV, 12-hourly

or alternatively, on its own:

- **Clindamycin**: 10 mg/kg (max 450 mg) IV, 8-hourly

### References


CHAPTER 5
Eye infections

5.1 Cellulitis around the eye (periocular cellulitis)

It is common to define cellulitis around the eye in terms of the orbital septum, the thin fascia that separates the eyelid from the orbit. Infections are called “preseptal” if they are anterior to the orbital septum and “orbital” if they are post-erior (i.e., inside the orbit). While this is anatomically logical, there is not much evidence that the distinction is valid clinically. Furthermore, preseptal cellulitis is also sometimes called periorbital cellulitis, so that the term “periorbital cellulitis” (literally around the orbit) is used to refer to cellulitis only in front of the septum, while the term “orbital cellulitis” is used for cellulitis within the orbit. It is not surprising that physicians get confused.

It is probably more useful for clinicians to think of cellulitis around the eye (periocular cellulitis) in terms of the likely cause and the severity, since these will determine treatment. Cellulitis around the eye may be secondary to trauma (a scratch, insect bite, or penetrating skin injury), may spread from infected skin (impetigo, pyoderma, chicken pox), may be bloodborne (as with Hib infections), or may spread from the paranasal sinuses. These generally have distinct clinical presentations. We will defy convention, and define cellulitis around the eye in terms of the likely etiology, based on the clinical presentation.

Local periocular cellulitis

Cellulitis of the eyelid, without proptosis or ophthalmoplegia, and without high fever or systemic illness, is likely to be caused by local introduction of organisms through trauma or spread from infected skin. Most children are <5 years old, and the most common organisms are *Staphylococcus aureus* and *Streptococcus pneumoniae* (group A streptococcus).1–3

If the child is well, and has been immunized against Hib, we recommend:

- cefuroxime 10 mg/kg (max 500 mg) orally 12-hourly OR
- cephalaxin 25 mg/kg (max 1 g) orally, 8-hourly OR
- amoxicillin + clavulanate 22.5 + 3.2 mg/kg (max 875 + 125 mg) orally, 12-hourly

If the child is ill enough to require parenteral therapy, we recommend to take blood cultures (to exclude hematogenous spread) and perform a CT scan to exclude sinusitis-associated infection.

We recommend:

- cefotaxime 50 mg/kg (max 2 g) IV, 8-hourly OR
- ceftriaxone 50 mg/kg (max 2 g) IV, daily

When improved, we recommend:

- amoxicillin + clavulanate 22.5 + 3.2 mg/kg (max 875 + 125 mg) orally, 12-hourly OR
- clindamycin 10 mg/kg (max 450 mg) orally, 8-hourly

If the child needs parenteral therapy and if, because of a local lesion such as a stye, dacryocystitis, impetigo, or a wound, staphylococcal infection is suspected, we recommend:

- di/fluc/o/na/clin 50 mg/kg (max 2 g) IV, 6-hourly OR
- cefazolin 15 mg/kg (max 600 mg) IV, 8-hourly OR (if cMRSA likely)
- clindamycin 10 mg/kg (max 450 mg) IV, 8-hourly

Deep orbital (sinusitis-associated) cellulitis

The paranasal sinuses surround the orbit: the roof of the orbit is the floor of the frontal sinus, the floor
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of the orbit is the roof of the maxillary sinus, and the ethmoid and sphenoid sinuses are the sides. Infection of the sinuses can readily spread through the bones to the orbit behind the eye. Here they cause erythema, swelling, pain and may or may not cause fever and systemic toxicity.1–4 The classical clinical presentation is with proptosis, ophthalmoplegia, particularly of upward gaze, chemosis, and often reduced visual acuity.1–4 Because the paranasal sinuses are rudimentary in infancy, and develop later, most affected children are >5 years old.1–4 Affected children commonly have a sub-periosteal abscess, adjacent to the ethmoid sinus in young children and to the frontal sinus in older children.2,3

The diagnosis is initially clinical, but CT scan is necessary to determine whether or not there is an associated sub-periosteal abscess and the need for drainage.1,2 In addition, there may be intracranial extension (see Section 10.2, p. 142).

Drainage of the sinuses or of an orbital, sub-periosteal, or intracranial abscess may be required, and we recommend consulting an ENT surgeon, and if necessary a neurosurgeon.

Causative agents include untypeable Haemophilus influenzae, S. pneumoniae, S. aureus, aerobic Gram-negative bacteria, and anaerobes.1,2

We recommend:

di/flucl/oxa/nafcillin 50 mg/kg (max 2 g) IV, 6-hourly OR
cefazolin 25 mg/kg (max 1 g) IV, 8-hourly (OR if cMRSA likely)
clindamycin 10 mg/kg (max 450 mg) IV, 8-hourly
PLUS EITHER
ceftaxime 50 mg/kg (max 2 g) IV, daily OR
ceftriaxone 50 mg/kg (max 2 g) IV, 8-hourly

When improved, use:

amoxicillin + clavulanate 22.5 + 3.2 mg/kg (max 875 + 125 mg) orally, 12-hourly OR
clindamycin 10 mg/kg (max 450 mg) orally, 8-hourly

Bacteremia-associated periocular cellulitis

In the days before H. influenzae type b (Hib) immunization, and in countries where Hib vaccine is not routine, the most common presentation of cellulitis around the eye was in association with Hib bacteremia. Children were usually infants <1 year old, and almost always <4 years, and presented with swelling around the eye with a peculiar purple (“violaceous”) color.1–3,5 They were usually highly febrile, toxic, and had high peripheral blood white cell counts. Hib was by far the most common cause, not uncommonly associated with Hib meningitis.1–3,5 Hib cellulitis has virtually disappeared following the introduction of universal Hib immunization.5

An identical clinical picture can be seen rarely with S. pneumoniae.6 In the post-Hib immunization era, bacteremia-associated periocular cellulitis is described rarely with S. pneumoniae, group A streptococcus, other streptococci, and untypeable H. influenzae.7,8 Where bacteremia seems clinically likely, we recommend taking blood cultures and admitting the child to hospital for IV antibiotics.

We recommend:

cefotaxime 50 mg/kg (max 2 g) IV, 8-hourly OR
ceftriaxone 50 mg/kg (max 2 g) IV, daily

Recurrent eyelid swelling

It is rare to get recurrent infectious cellulitis. Recurrent eyelid swelling is often diagnosed and treated as recurrent cellulitis. It is, however, much more likely to have an allergic basis, either as a manifestation of allergic conjunctivitis and/or as a form of angioedema.9,10 We advise referral to an allergist for investigation for atopy.

5.2 Conjunctivitis in infants and children

Acute conjunctivitis is the most common disorder of the eye seen by the primary care practitioner.2,11 We will consider neonatal conjunctivitis separately (see Section 5.3, p. 45). Several studies have documented that bacterial conjunctivitis, with or without otitis media, predominantly occurs in children <6 years of age.11–16 It is difficult to distinguish viral from bacterial conjunctivitis clinically.

Organisms causing acute conjunctivitis in children

Outside the neonatal period, the commonest pathogens detected from children with acute conjunctivitis are untypeable H. influenzae (42–52%), adenovirus
(13–20%), and *S. pneumoniae* (7–17%).\textsuperscript{11–16} A Gram stain and culture is necessary to distinguish and identify bacterial conjunctivitis, while special tests are needed to identify adenoviruses or herpes simplex virus (HSV) rapidly.

**Clinical features of acute conjunctivitis in children**

Most childhood conjunctivitis is mild, self-resolving, and viral, and requires no treatment. There are some recognizable clinical syndromes, however, which have treatment or public health implications.

**Acute hemorrhagic conjunctivitis**

Acute hemorrhagic conjunctivitis is most commonly caused by enteroviruses, including Coxsackieviruses, but can also be caused by adenovirus type 11. It is a highly contagious infection and usually occurs in epidemics.\textsuperscript{16} Most reported cases occur in Asia, but several epidemics have been reported in Africa, the Caribbean, South America, Central America, and North America.\textsuperscript{16} Patients present with sudden development of hyperemic conjunctiva, sub-conjunctival hemorrhages, chemosis of the conjunctiva, lid swelling, excessive tearing, photophobia, and pain. The major symptoms last 3–5 days, and resolve over 10 days. Neurologic complications have been reported in about 1 in 10,000 cases of enterovirus type 70 infection, ranging from transient, mild cranial nerve palsies to permanent flaccid paralysis of a limb (monoplegia) or limbs resembling poliomyelitis.\textsuperscript{16}

**Conjunctivitis-otitis syndrome**

*H. influenzae* (untypeable) is the commonest organism isolated, and can be grown from the eyes of 42–52% of children with acute conjunctivitis.\textsuperscript{12–16} Clinically it can cause the “conjunctivitis–otitis syndrome.” Children characteristically develop low grade fever and mild respiratory symptoms, including cough and mucopurulent nasal discharge, followed after several days, by eye pain and discharge. Some children develop ear pain, but otitis is asymptomatic in about 60% of children.\textsuperscript{11,17} Sometimes a child presents with otitis media and develops purulent conjunctivitis later.\textsuperscript{11,17} In one study, *H. influenzae* was isolated from 73% of conjunctival cultures taken from children with both otitis and conjunctivitis.\textsuperscript{17}

**Gonococcal conjunctivitis**

Gonococcal conjunctivitis is well recognized in neonates, but the diagnosis may not be considered in older children. Patients present with an abrupt onset of copious, purulent discharge; eyelid edema; and fever.\textsuperscript{18} As in neonates, this organism can cause ulceration and perforation of the cornea, leading to blindness.\textsuperscript{16,18} Because the organism is usually transmitted through sexual contact, all under-age children with gonococcal conjunctivitis should be investigated for possible sexual abuse. An outbreak of gonococcal conjunctivitis occurred when urine was applied to the eyes of patients with enteroxiral conjunctivitis as a folk remedy.\textsuperscript{19} Sexually active adolescents can contract gonococcal conjunctivitis and should be evaluated for other sites of infection, as well as for other sexually transmitted diseases.\textsuperscript{20}

**HSV conjunctivitis**

HSV conjunctivitis may occur with primary infection or with recurrence. The peak age of primary infection is 1–5 years.\textsuperscript{16,21} Neonatal HSV conjunctivitis is an emergency because of the risk of encephalitis (see p. 145). Recurrent HSV infections typically occur in older children and adults.\textsuperscript{16} The diagnosis is most likely to be made if there are vesicles on the lid or face, or gingivostomatitis or keratitis. Corneal involvement with the classic dendritic appearance is present in 50% of patients.\textsuperscript{16} The diagnosis can usually be made clinically, but if the diagnosis is in question, viral cultures and antigen detection tests (immunofluorescence, ELISA, polymerase chain reaction [PCR]) can be performed.\textsuperscript{16}

**Meningococcal conjunctivitis**

Two types of meningococcal conjunctivitis have been described: primary, which can be invasive or non-invasive, and secondary, which occurs after systemic infection.\textsuperscript{22,23} Complications of primary meningococcal conjunctivitis include corneal ulceration, keratitis, sub-conjunctival hemorrhage, iritis, and systemic meningococcal disease.\textsuperscript{22,23} Patients present with acute, purulent discharge, and sometimes fever, similar to gonococcal conjunctivitis.\textsuperscript{22,23} The Gram stain reveals Gram-negative diplococci.\textsuperscript{22,23} In a review of children and adults with meningococcal conjunctivitis,\textsuperscript{22} two-thirds of which was unilateral, 18% of patients developed systemic infection, which had a mortality
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over 13%. Systemic antibiotics should be administered, because topical antibiotics are ineffective, and chemoprophylaxis should be offered to contacts (see p. 138).

Pharyngoconjunctival fever
Adenovirus is identified as the pathogen in about 20% of cases of conjunctivitis. It can be detected by culture, immunofluorescence, ELISA or PCR, but as the tests are not routinely performed, the true incidence may be higher than 20%. Adenovirus infection may be associated with either pharyngoconjunctival fever or epidemic keratoconjunctivitis. Outbreaks of pharyngoconjunctival fever have been associated with swimming in poorly chlorinated swimming pools and contaminated ponds. It manifests with high fever, pharyngitis, follicular conjunctivitis with chemosis and hyperemia, and bilateral preauricular adenopathy. It typically takes between 4 days and 2 weeks for symptoms to resolve. Epidemic keratoconjunctivitis is a conjunctivitis with keratitis, and sometimes small, petechial hemorrhages, which presents with pain, photophobia and decreased vision, and sometimes associated pharyngitis and rhinitis. Hazy, grayish-white subepithelial infiltrates can be found later in the course of illness, and may not resolve for several months. The conjunctival and eyelid swelling can be marked, and patients with severe cases may develop inflammatory pseudomembranes. Severe cases may be mistaken for preseptal or periorbital cellulitis.

Brazilian purpuric fever
H. aegyptius can cause conjunctivitis associated with overwhelming septicemia with purpura, indistinguishable from meningococcal infection. It has only been described in South America and Australia.

Treatment of acute conjunctivitis in children

Question | For children beyond the neonatal period with acute conjunctivitis do topical antibiotics, compared with no treatment or placebo, hasten recovery?

Literature review | We found six RCTs, although only two were in children, and a Cochrane review.

In considering topical antibiotic use, we need to distinguish children with proven bacterial conjunctivitis from those who present to their primary care physician with acute conjunctivitis.

A study of 102 children with bacterial conjunctivitis (61 H. influenzae, 22 S. pneumoniae) found that 62% of the children given topical polymyxin-bacitracin but only 28% of the placebo group had resolved at 3–5 days. By 8–10 days, 91 and 72% respectively had resolved, a difference which was not statistically significant although the organism persisted longer in the placebo group.

An RCT in general practice found that antibiotics did not affect the severity of symptoms of acute infective conjunctivitis in adults and children, but antibiotics did reduce the duration of moderate symptoms from 4.8 to 3.3 days. In the same study, only 53% of patients used antibiotics if a delayed prescription was given, yet the duration of symptoms in the delayed group was 3.9 days, suggesting this is a reasonable compromise between immediate and no antibiotics.

In contrast, an RCT of 326 children presenting to their family doctor with acute conjunctivitis and randomized to topical chloramphenicol or placebo found that 86 and 83% had resolved by 7 days, with no significant difference between treatment groups. Recurrences within 6 weeks were equally common in each group.

A Cochrane review of the treatment of bacterial conjunctivitis in adults and children found that topical antibiotics were of benefit early (days 2–5) in improving clinical (RR 1.24, 95% CI 1.05–1.45) and microbiological (RR 1.77, 95% CI 1.23–2.54) remission rates. These early advantages were reduced by days 6–10, but still significant. Most cases, however, resolved spontaneously, with clinical remission being achieved by days 2–5 in 65% (95% CI 59–70) of those receiving placebo. No serious outcomes were reported in either the active or placebo arms of these trials, indicating that important, sight-threatening complications are an infrequent occurrence.

Question | In children beyond the neonatal period with acute conjunctivitis do oral antibiotics compared with topical antibiotics or placebo hasten recovery and/or prevent otitis media?

Literature review | We found one RCT comparing oral with topical antibiotics and one RCT of oral antibiotics versus placebo.
An RCT of 80 children found that 3 days of oral cefixime was not more effective than 7 days of topical polymyxin-bacitracin in either the eradication of conjunctival colonization with respiratory pathogens or the prevention of acute otitis media in children with acute bacterial conjunctivitis.30

An RCT of children with conjunctivitis found that oral amoxicillin reduced the proportion infected with untypeable _H. influenzae_ who developed acute otitis media, but did not eradicate the organism.31 The study did not evaluate duration of eye symptoms.

**We recommend topical antibiotics for proven bacterial conjunctivitis, but not routinely for childhood conjunctivitis.**

**Treatment of viral and presumed viral conjunctivitis**

For most viral conjunctivitis, including adenoviral and enteroviral conjunctivitis, treatment is supportive.16 Cold compresses, artificial tears, and topical vasoconstrictors may provide comfort. Studies comparing antiviral agents and anti-inflammatory medications with artificial tears show no significant difference between these medications and artificial tears.32,33 Topical steroids should be avoided because they have significant side effects, such as superinfection, glaucoma, and cataract.32 Topical steroids also may exacerbate a missed diagnosis of herpes conjunctivitis, may enhance adenoviral replication, and may increase the duration of adenoviral shedding.32 Topical antibiotics are usually unnecessary, as secondary bacterial infections are rare.16,32 We recommend using saline washes alone for mild cases of childhood conjunctivitis.

Specific therapy is available for conjunctivitis due to HSV or associated with zoster (see below).

**Treatment of HSV conjunctivitis**

Topical antiviral agents, such as acyclovir, are typically used to treat HSV conjunctivitis occurring in children well beyond the neonatal period16,21 (for neonates, systemic therapy is essential). Oral or IV acyclovir can be used in severe cases or to suppress recurrent lesions,34 but recurrent HSV keratoconjunctivitis is much more common in adults.16,33 Steroids should be avoided, as they can aggravate the infection.16

**Treatment of ophthalmic varicella zoster virus (VZV) infection**

A mild conjunctivitis is frequent with chicken pox (primary infection with VZV) and usually requires no specific treatment.

Ophthalmic zoster (herpes zoster ophthalmicus) results from reactivation of latent VZV in the first branch of the trigeminal nerve (Vth nerve). It accounts for approximately 15% of all zoster cases. Without specific treatment 50–70% of patients with ophthalmic zoster will develop ocular complications from direct viral invasion (superficial keratitis including punctate and dendritic keratitis and conjunctivitis), secondary inflammation and alteration of autoimmune mechanisms (stromal keratitis, uveitis, scleritis, and episcleritis), or neurotrophic disorders (neurotrophic keratitis).35,36 Treatment should be with oral or IV antivirals and should be started as soon as the diagnosis is suspected. Oral acyclovir is highly effective in decreasing pain and in reducing the incidence of ocular complications, such as corneal damage and anterior uveitis.37 Oral famciclovir38 and oral valaciclovir39 are as effective in adults as oral acyclovir, but are not recommended for children <12 years. Topical acyclovir alone is insufficient.40 An ophthalmologist should be consulted.

For children, we recommend hospital admission for an ophthalmologic opinion and for IV therapy:

- **acyclovir 10 mg/kg IV, 8-hourly**

For older children and where compliance is good, it is possible to use:

- **acyclovir 20 mg/kg (max 800 mg) orally, 5 times daily for 7 days OR**
- **famiciclovir (12 years or older) 250 mg orally, 8-hourly for 7 days OR (if immunocompromised)**
- **famiciclovir 500 mg orally, 8-hourly for 10 days OR**
- **valaciclovir (12 years or older) 1 g orally, 8-hourly for 7 days**

**Treatment of bacterial and presumed bacterial conjunctivitis**

For severe cases, and where bacterial conjunctivitis is confirmed,26–29 we recommend:
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 chloramphenicol 0.5% eye drops, 1–2 drops 2–6-hourly, for 2–3 days OR
 chloramphenicol 1% eye ointment 1.5 cm 3-hourly or at bedtime (drops by day) OR
 polymyxin, neomycin, bacitracin eye ointment 6–12-hourly OR
 framycetin 0.5% eye drops, 2 drops every 1–2 hours initially, then 8-hourly as infection improves

Gentamicin, tobramycin, and quinolone eye drops are substantially more expensive than the recommended drugs and are generally unnecessary for empiric treatment.

5.3 Neonatal eye infections

Most neonatal conjunctivitis in industrialized countries is chemical, due to prophylaxis or other irritants. On the other hand, there are four major diagnoses not to be missed in the newborn baby presenting with conjunctivitis: gonorrhea, chlamydia, HSV, and panophthalmitis.

Chemical conjunctivitis in neonates

Conjunctivitis occurring within the first 24 hours of life is most likely an irritant reaction to ocular prophylaxis. This is most often seen with silver nitrate and less often with erythromycin or tetracycline prophylaxis. The typical clinical course of chemical conjunctivitis is presentation of mild, purulent conjunctivitis within the first 24 hours of life and resolution within 48 hours. Gram stain of conjunctival scrapings shows no bacteria. No specific treatment is needed.

Gonococcal ophthalmia neonatorum

The typical presentation of gonococcal conjunctivitis is with sudden, severe, grossly purulent conjunctivitis in the first 3–5 days of life and sometimes at birth. There may or may not be a history of maternal vaginal discharge. If not recognized, this organism can rapidly progress within 24 hours to ulceration and perforation of the globe. If gonococcus is suspected, a culture and Gram stain of conjunctival scrapings should be obtained. Concomitant specimens for Chlamydia should also be obtained. A presumptive diagnosis of gonococcal conjunctivitis is made by identifying Gram-negative diplococci in conjunctival scrapings and treatment should be started.

We recommend:

ceftriaxone 25–50 mg/kg (max 125 mg) IV or IM, as single dose (unless jaundiced)

Ceftriaxone displaces bilirubin from albumin and can exacerbate jaundice. If jaundiced, we recommend:

cefotaxime 25 mg/kg IV, 6-hourly for 7 days

For patients with anaphylactic allergy to penicillin and/or cephalosporins, we recommend:

ciprofloxacin 10 mg/kg (max 400 mg) IV, 12-hourly for 5 days

Gonococcal conjunctivitis can occur in older children and adolescents sporadically and in epidemics. The rare sporadic cases outside these areas should be treated in consultation with an ophthalmologist, and the possibility of child sexual abuse must be considered. Topical antimicrobial treatment alone is ineffective and topical antibiotics are not required when systemic therapy is used, although saline irrigation reduces discomfort and purulent discharge. For systemic therapy, because of penicillin resistance, we recommend:

ceftriaxone 50 mg/kg (max 1 g) IM or IV, as a single dose

Treatment of meningococcal conjunctivitis

For the treatment of acute meningococcal conjunctivitis, systemic antibiotics should be administered, because topical antibiotics are ineffective, and chemoprophylaxis should be offered to contacts (see p. 138). We recommend:

benzylpenicillin 30 mg (50,000 U)/kg (max 1.2 g or 2 million U) IV, 4-hourly for 5 days

For patients with penicillin allergy (excluding anaphylactic allergy), we recommend:

ceftriaxone 100 mg/kg (max 4 g) IV, daily for 5 days OR
cefotaxime 50 mg/kg (max 2 g) IV, 6-hourly for 5 days

For patients with anaphylactic allergy to penicillin and/or cephalosporins, we recommend:

ciprofloxacin 10 mg/kg (max 400 mg) IV, 12-hourly for 5 days

5.3 Neonatal eye infections

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Gonococcal ophthalmia neonatorum

The typical presentation of gonococcal conjunctivitis is with sudden, severe, grossly purulent conjunctivitis in the first 3–5 days of life and sometimes at birth. There may or may not be a history of maternal vaginal discharge. If not recognized, this organism can rapidly progress within 24 hours to ulceration and perforation of the globe. If gonococcus is suspected, a culture and Gram stain of conjunctival scrapings should be obtained. Concomitant specimens for Chlamydia should also be obtained. A presumptive diagnosis of gonococcal conjunctivitis is made by identifying Gram-negative diplococci in conjunctival scrapings and treatment should be started.

We recommend:

ceftriaxone 25–50 mg/kg (max 125 mg) IV or IM, as single dose (unless jaundiced)

Ceftriaxone displaces bilirubin from albumin and can exacerbate jaundice. If jaundiced, we recommend:

cefotaxime 25 mg/kg IV, 6-hourly for 7 days

For patients with anaphylactic allergy to penicillin and/or cephalosporins, we recommend:

ciprofloxacin 10 mg/kg (max 400 mg) IV, 12-hourly for 5 days

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Conjunctivitis occurring within the first 24 hours of life is most likely an irritant reaction to ocular prophylaxis. This is most often seen with silver nitrate and less often with erythromycin or tetracycline prophylaxis. The typical clinical course of chemical conjunctivitis is presentation of mild, purulent conjunctivitis within the first 24 hours of life and resolution within 48 hours. Gram stain of conjunctival scrapings shows no bacteria. No specific treatment is needed.

Gonococcal ophthalmia neonatorum

The typical presentation of gonococcal conjunctivitis is with sudden, severe, grossly purulent conjunctivitis in the first 3–5 days of life and sometimes at birth. There may or may not be a history of maternal vaginal discharge. If not recognized, this organism can rapidly progress within 24 hours to ulceration and perforation of the globe. If gonococcus is suspected, a culture and Gram stain of conjunctival scrapings should be obtained. Concomitant specimens for Chlamydia should also be obtained. A presumptive diagnosis of gonococcal conjunctivitis is made by identifying Gram-negative diplococci in conjunctival scrapings and treatment should be started.

We recommend:

ceftriaxone 25–50 mg/kg (max 125 mg) IV or IM, as single dose (unless jaundiced)

Ceftriaxone displaces bilirubin from albumin and can exacerbate jaundice. If jaundiced, we recommend:

cefotaxime 25 mg/kg IV, 6-hourly for 7 days

For patients with anaphylactic allergy to penicillin and/or cephalosporins, we recommend:
saline several times a day until the purulence subsides. The mother and her sexual contacts should be treated for gonorrhea. The patient also should be evaluated for disseminated infection, such as arthritis, meningitis, or sepsis.

Coinfection with *Chlamydia trachomatis* and *Neisseria gonorrhoeae* is common in some areas, and we recommend testing any baby with gonorrhea for chlamydia also.

### Neutonal chlamydia conjunctivitis

*C. trachomatis* can cause unilateral or bilateral mucopurulent neonatal conjunctivitis, classically at 5–14 days old, although extremes of 1–60 days have been described. The presentation can vary from mild to moderate conjunctival erythema and from scant, mucoid discharge to copious, purulent discharge. Eyelid edema, chemosis, or pseudomembrane formation may also be present.

The diagnosis can be made by both culture and rapid techniques. Special Dacron-tipped swabs are needed for culture, and epithelial cells must be collected, not just exudate. Other tests using rapid techniques like PCR or ELISA are sensitive and specific.

Up to half of untreated children with chlamydia ophthalmia will develop chlamydia pneumonia, and so the recommended treatment is with oral not topical antibiotics. A preliminary study of azithromycin for neonatal disease had treatment failures and was inconclusive. We recommend:

**erythromycin base or ethylsuccinate 10 mg/kg orally, 6-hourly for 14 days**

There have been unproven concerns about the relationship between erythromycin and pyloric stenosis, but even if erythromycin genuinely causes pyloric stenosis in a proportion of babies, this may be a class effect of macrolides. The seriousness of chlamydia eye and pulmonary disease is a major consideration in our recommendation.

Sometimes a second course of erythromycin is needed, as the efficacy of erythromycin is approximately 80%. Topical antibiotics are ineffective and unnecessary. The mother and her sexual contacts should be treated for chlamydia.

### Neonatal HSV conjunctivitis

Neonatal HSV conjunctivitis classically presents from day 5 to day 14, but can be present at birth. Clinically, it can be unilateral or bilateral and there may be ipsilateral eyelid edema and serous discharge. If characteristic, blistering herpetic lesions develop on the lid or face, or if there are lesions in the mouth, or if there are corneal lesions, the diagnosis may be apparent. Otherwise, there are no clinical distinguishing features of HSV conjunctivitis. Without treatment, however, 70% of neonates with HSV disease restricted to the skin, eye, or mouth (SEM) will progress to disseminated and/or CNS infection with a 50–85% mortality by 1 year of age. With early diagnosis, HSV conjunctivitis is usually restricted to local disease. The prognosis of local (SEM) HSV infection is far better, but 2–12% still have neurologic impairment, indicating occult CNS disease or treatment failure. Clearly, it is vital to make the diagnosis and treat as early as possible.

We recommend:

**acyclovir 20 mg/kg, IV, 8-hourly for 14 days (21 days when CNS involvement proven)**

### Neonatal conjunctivitis from *Staphylococcus aureus* and other bacteria

Many other organisms can be grown from the eyes of babies with ophthalmia neonatorum, including *S. aureus*, *S. pneumoniae*, viridans streptococci, other *Streptococcus* species, *H. influenzae*, *Escherichia coli*, *Pseudomonas* species, *Klebsiella* species, *Enterobacter* species, *Proteus* species, viruses, and others. Their role in neonatal conjunctivitis is controversial, and particularly that of *S. aureus*, which can be cultured frequently from the eyes of asymptomatic neonates. Most infections caused by these organisms can be treated with topical antibiotics alone or even with saline without antibiotics.

*Pseudomonas aeruginosa* needs special consideration. *P. aeruginosa* conjunctivitis can be mild (sticky eye), or babies can present with edema and erythema of the eyelids and purulent discharge, which can be associated with pannus formation and with endophthalmitis. For babies with mild conjunctivitis associated with *Pseudomonas*, it is possible to use topical antibiotics, but an ill baby should be treated with systemic antibiotics. On the other hand, isolation
of *P. aeruginosa* from the eyes of a well neonate with mild conjunctivitis is not an indication for systemic antibiotics, because the risk of progression is extremely low.49,50

Other organisms apart from *Pseudomonas* that can cause neonatal endophthalmitis include group B streptococcus, other Gram-negative bacilli, and fungi, notably *Candida*.49,50 The organism may be isolated from eye swab, blood, or cerebrospinal fluid, but if there is doubt, it may be necessary to take an intravitreal specimen from the eye for Gram stain and culture. An ophthalmologic consultation is obviously essential for diagnosis and treatment, which may involve subconjunctival or intravitreal injections, in addition to systemic antibiotics, because of poor penetration.49,50

5.4 Chronic conjunctivitis in neonates and older children

**Nasolacrimal duct obstruction**

Congenital nasolacrimal duct obstruction affects up to 20% of all newborns and is the commonest cause of chronic eye discharge in babies.51–53 Affected children present with epiphora (excessive tearing), chronic or recurrent conjunctivitis, or eye discharge, which may progress to frank cases of acute dacryocystitis. Management ranges from watchful waiting to simple probing to probing with Silastic intubation to dacryocystorhinostomy. An observational study found that 964 of 4729 infants (20%) had evidence of defective lacrimal drainage (documented with a fluorescein disappearance test) and 95% of these babies were symptomatic with epiphora during the first month of life.53 Spontaneous remission of epiphora occurred throughout the year, and 96% of cases had resolved before patients reached the age of 1 year.53

It is often recommended that most babies with nasolacrimal duct obstruction can be treated with massage alone, although there are no RCTs to say whether this actually speeds resolution.53–56 More severe cases may need probing or saline irrigation by an ophthalmologist, which have been shown to be as effective as each other.56 By the second year of life, probing has marginally better efficacy than watchful waiting, but 60% still resolve spontaneously.57

**Chronic dacryocystitis**

Chronic dacryocystitis means chronic inflammation of the lacrimal sac. It is really just a rather grand name for children with congenital nasolacrimal duct obstruction, but with chronic mucopurulent discharge. In a paper from Austria, bacteria could be grown from 73% of babies with chronic dacryocystitis; the organisms grown most frequently were *S. pneumoniae* (35%) and *H. influenzae* (20%), followed by *Pseudomonas*, viridans streptococci, and *Morganella*.58 No staphylococci were isolated. In contrast, a recent Polish paper59 found staphylococci (*S. aureus* and coagulase negative staphylococci) were the commonest isolates. There are no RCTs of antibiotic therapy, but in the Austrian paper, initial therapy with topical bacitracin and neomycin was associated with resolution in 82.5% of patients.58

**Trachoma (chronic *Chlamydia trachomatis* conjunctivitis)**

Chronic *C. trachomatis* infection can produce trachoma, a form of chronic conjunctivitis which is a leading cause of blindness in the developing world. Trachoma is a disease of poverty that thrives in remote, marginalized, and displaced populations. Clinically, trachoma can be divided into its acute (active) and chronic or late-stage manifestations, but acute and chronic signs can occur at the same time in the same individual. In areas where it is endemic, repeated episodes of active disease occur, particularly during childhood, and are probably required for later development of the chronic sequelae. Following repeated infections, the upper tarsal conjunctiva becomes scarred. As scar tissue contracts, it shortens the inner surface of the upper lid, causing the eyelashes to turn in (entropion) and brush against the transparent cornea. This contact between eyelashes and the surface of the eye is called trichiasis: movement of the eye or eyelids damages the corneal epithelium. Corneal opacification and resulting blindness probably develops primarily as a result of this trauma and secondary bacterial corneal infection.

A Cochrane review of antibiotic treatment of trachoma found 15 RCTs with a total of 8678 participants.61 The review did not show immediate benefit in the resolution of active trachoma from either oral or topical antibiotics compared with placebo/no treatment, but did show reduced infection at both 3 and 12 months after treatment.61 Oral antibiotics were no more effective than topical antibiotics.61
A Gambian RCT involved 1803 villagers, 16% of whom had active trachoma. They were randomized to receive either three doses of azithromycin at weekly intervals or daily topical tetracycline over 6 weeks. Two months after treatment, the prevalence of trachoma was 4.6 and 5.1% in the azithromycin and the tetracycline groups, respectively (OR 1.09; 95% CI 0.53–2.02). However, 12 months post-treatment there were fewer new prevalent cases, 7.7%, in the azithromycin group compared to 16% in the tetracycline group (OR 0.52; 95% CI 0.34–0.80) and trachoma resolution was significantly better with azithromycin (OR 2.02; 95% CI 1.42–3.50). The authors concluded that azithromycin is easy to administer and may be more successful in trachoma than prolonged topical treatment.

There is evidence that insecticide spray as a fly control measure reduces the incidence of trachoma significantly, while face-washing may be beneficial. The diagnosis is primarily clinical, because growing the organism or detecting it by antigen detection, PCR, or ligase chain reaction tests is too expensive in the field. Clinical grading with the WHO simplified system can be highly repeatable provided graders are adequately trained and standardized.

For neonates (inclusion conjunctivitis) and children under 6 kg, treat with oral erythromycin as shown above (see p. 46).

For children over 6 kg with acute or chronic trachoma, we recommend:

**azithromycin 20 mg/kg (max 1 g) orally, as a single dose**

The WHO has set a target of global elimination of trachoma as a public health problem by the year 2020. Community screening programs have been instituted but are difficult because trachoma typically affects the most medically underserved populations.

### 5.5 Infections of the eyelids

#### Blepharitis

Blepharitis is an inflammation of the lid margins. It occurs most commonly as a complication of seborrheic dermatitis of the scalp and eyebrows. Treatment of the seborrhea, e.g., with coal tar, is usually sufficient.

Blepharitis can be associated with culture of *S. aureus* and other staphylococci, but their role is uncertain. There are no RCTs comparing treatment with placebo, but we found two RCTs comparing different topical antibiotics for bacterial blepharitis. Topical ciprofloxacin is superior to topical rifamycin or topical fusidic acid. For acute bacterial blepharitis, we recommend:

**ciprofloxacin ophthalmic solution 0.3% one drop to each eye 2-hourly while awake for 2 days, then 4-hourly while awake for 5 days**

#### Blepharokeratoconjunctivitis

Chronic or recurrent blepharitis is often associated with keratoconjunctivitis. Blepharokeratoconjunctivitis is a chronic inflammatory disorder of children, causing a spectrum of clinical manifestations, from chronic eyelid inflammation, recurrent chalazia, and conjunctival and corneal phlyctenules to neovascularization and scarring. It is sometimes called phlyctenular conjunctivitis. There are no RCTs comparing the use of topical antibiotics with placebo or with oral antibiotics. There are only observational reports of the use of oral erythromycin or tetracyclines. The antibiotics may be acting as anti-inflammatory agents, since topical and even oral corticosteroids are often used and appear to control inflammation.

#### Chalazion

A chalazion is a sterile lipogranulomatous inflammatory mass, which causes a bulge in the eyelid. It is non-tender and persists for 2 weeks or more. It is not infectious.
Dacryoadenitis
Dacryoadenitis is an infected lacrimal gland, causing swelling of the outer portion of the upper eyelid.\textsuperscript{73,74} It can be associated with viral infections including EBV, when it causes characteristic bilateral, painless swelling of the upper lids (Hoagland’s sign).\textsuperscript{73,74} Bacterial dacryoadenitis, usually due to \textit{S. aureus}, can present as an acute, painful inflammation, and the eyeball may be red and swollen.\textsuperscript{73} Children with severe infections may require hospital admission. For severe infections, we recommend:

- **di/flucl/oxa/nafcillin** 25 mg/kg (max 1 g) orally or IV, 6-hourly \textbf{OR}
- **cephalexin** 25 mg/kg (max 1 g) orally, 8-hourly \textbf{OR}
- **cefazolin** 15 mg/kg (max 600 mg) IV, 8-hourly

Dacryocystitis
Acute dacryocystitis, which is an infection of the lacrimal sac, can cause a red, painful swelling of the medial canthus.\textsuperscript{74} Children may be systemically very unwell and need hospitalization. The commonest cause is \textit{S. aureus}, but \textit{S. pyogenes}, Gram-negative and anaerobic organisms are described.\textsuperscript{74} Referral to an ophthalmologist and consideration of duct probing or external drainage is recommended. Systemic antibiotic therapy is indicated and is best guided by results of Gram stain and culture.

Pending results, we recommend:

- **di/flucl/oxa/nafcillin** 50 mg/kg (max 2 g) IV, 6-hourly \textbf{OR}
- **cefazolin** 15 mg/kg (max 600 mg) IV, 8-hourly

Meibomian abscess (internal hordeolum)
Meibomian abscess (internal hordeolum) is an infection, usually a staphylococcal abscess, of a long sebaceous gland in the eyelid called a meibomian gland.\textsuperscript{73} As these abscesses seldom discharge spontaneously, warm compresses and oral anti-staphylococcal antibiotics are recommended, particularly if there is accompanying cellulitis. Surgical incision and curettage may also be necessary. Topical antibiotics are not indicated. We recommend:

- **di/flucl/oxa/nafcillin** 12.5 mg/kg (max 500 mg) orally, 6-hourly \textbf{OR}
- **cephalexin** 12.5 mg/kg (max 500 mg) orally, 6-hourly

Stye (external hordeolum)
A stye is a bacterial infection of a hair follicle on the eyelid, usually caused by \textit{S. aureus}.\textsuperscript{73} Treatment is not usually necessary as it is self-limiting and annoying rather than painful. Warm compresses may soothe. If infection persists, we recommend:

- polymyxin, neomycin, bacitracin eye ointment 6–12-hourly \textbf{OR}
- framycetin 0.5% eye drops, 2 drops every 1–2 hours initially, then 8-hourly as infection improves

5.6 Infections of the globe
Endophthalmitis
Endophthalmitis almost always occurs as a result of one of three mechanisms: following surgery, from a penetrating injury, or from metastatic bacteremic spread.\textsuperscript{75}

In adults, surgery is the commonest cause of endophthalmitis, mostly cataract surgery. In children, post-surgical endophthalmitis is rare,\textsuperscript{76} but can be sight-and even life-threatening.\textsuperscript{77}

Endophthalmitis can follow penetrating injuries. In one series, good results were obtained (visual acuity 20/200 in 67% of eyes) with early aggressive therapy, which included intravitreal antibiotics, and vitrectomy in two-thirds of cases.\textsuperscript{78} The commonest organisms were streptococci, staphylococci, and Gram-negative bacilli.\textsuperscript{78}

Endogenous bacterial endophthalmitis is rare, and occurs when bacteria from the bloodstream of a bacteremic person cross the blood-ocular barrier and multiply within the eye. The most common Gram-positive organisms from blood cultures are \textit{S. aureus}, group B streptococci, \textit{S. pneumoniae}, and \textit{Listeria monocytogenes}. The most common Gram-negative organisms are \textit{Klebsiella} spp., \textit{E. coli}, \textit{P. aeruginosa}, and \textit{Neisseria meningitidis}.\textsuperscript{79,80} Gram-negative organisms are responsible for the majority of cases reported from East Asian hospitals,\textsuperscript{80} but Gram-positive organisms are more common in North America and Europe.\textsuperscript{79} The visual outcome is poor with most cases leading to blindness in the affected eye. Many patients have extraocular foci of infection, with an
associated mortality rate of 5%. The condition is often misdiagnosed, and the outcome of endogenous bacterial endophthalmitis has not improved in 55 years.\textsuperscript{79}

Various forms of antibiotic therapy have been used including topical, intravenous, sub-conjunctival, and intravitreal.\textsuperscript{75} There have been few trials of prophylaxis or treatment. One RCT showed that giving prophylactic intravitreal vancomycin (1 mg) and ceftazidime (2.25 mg) at the time of operation compared with no intravitreal antibiotics improved the outcome for patients undergoing primary repair for globe injuries.\textsuperscript{81} Both groups received IV ciprofloxacin. The incidence of endophthalmitis was significantly lower in the intravitreal group (6%) than the control group (18%).\textsuperscript{81} A second RCT of prophylactic intraocular injection of clindamycin and gentamicin for penetrating eye injury was underpowered and showed only a trend to reduced endophthalmitis.\textsuperscript{82}

A multicenter RCT studied patients with a distinct clinical entity, post-cataract endophthalmitis. In this study, 420 patients with clinical endophthalmitis <6 weeks after cataract surgery or secondary intraocular lens implantation found that systemic antibiotics (ceftazidime and amikacin) did not improve visual acuity or media clarity at 9 months, compared with vitreal tap or vitrectomy. Vitrectomy was of no benefit, except in the sub-group of patients with initial light perception-only vision.\textsuperscript{83}

Patients with penetrating eye injuries and/or endophthalmitis require specialized management by an ophthalmologist, possibly including intravitreal antibiotics (see below). Antibiotic therapy should be guided by Gram stain of material obtained urgently at operation. If there is to be significant delay before obtaining advice or admitting the patient to a specialized unit, we recommend:

- **Ciprofloxacin** 15 mg/kg (max 750 mg) orally, as a single dose PLUS
- **Vancomycin** <12 years: 30 mg/kg; >11 years: 25 mg/kg (max 1.5 g) IV, as a single dose by slow infusion

Regimens that have been used for intravitreal therapy in adults include:

- **Vancomycin** 1 mg by intravitreous injection
- **Ceftazidime** 2.25 mg by intravitreous injection
- **Amikacin** 0.4 mg by intravitreous injection
- **Amphotericin B** 0.005 mg by intravitreous injection

The dose is repeated if there is not a complete response after 24–48 hours. A study suggested that the addition of intravitreal dexamethasone 0.4 mg to intravitreal antibiotic therapy might improve the outcome for post-operative endophthalmitis, although the difference did not reach statistical significance.\textsuperscript{84}

**Uveitis**
Uveitis refers to any intraocular inflammation. It may be anterior, involving the iris and ciliary body (iritocyclitis), or post-erior, involving the choroid and retina (chorioretinitis or choroidoretinitis).

**Iridocyclitis**
Iridocyclitis, particularly when chronic, is usually associated with juvenile arthritis and other inflammatory conditions, not infections.\textsuperscript{85} Rare exceptions of infections that can cause acute or chronic iridocyclitis include herpes viruses (EBV, HSV, HHV-6, VZV), borrelia (Lyme disease), and mycobacteria (\textit{Mycobacterium tuberculosis}, \textit{M. leprae}).

**Chorioretinitis**
Infectious chorioretinitis (or choroidoretinitis or retinochoroiditis) is most commonly due to infections acquired prenatally. The prenatal infections classically described as causing congenital chorioretinitis are toxoplasmosis,\textsuperscript{86} cytomegalovirus (CMV),\textsuperscript{87} and rubella,\textsuperscript{88} although congenital infection with lymphoctic choriomeningitis virus\textsuperscript{89} can also cause chorioretinitis. The chorioretinitis is usually associated with other signs of infection, such as intracerebral calcification and microcephaly or hydrocephalus.\textsuperscript{86–89}

**Cytomegalovirus chorioretinitis**
Congenital CMV chorioretinitis is usually present at birth, often in association with microcephaly and periventricular calcification, and almost always carries a grave neurologic prognosis.\textsuperscript{90} Its presentation may be delayed or it may reactivate later.\textsuperscript{91} Although ganciclovir treatment of CMV-infected neonates may reduce the incidence of deafness, it has no effect on retinitis.\textsuperscript{92}

CMV retinitis rarely occurs in immunocompromised patients with HIV infection, transplant
Eye infections

recipients, and patients with cancer. Oral valganciclovir is as effective as IV ganciclovir as induction therapy for HIV-infected adults with CMV retinitis,\textsuperscript{93} and can be used for maintenance therapy. There are no data yet on valganciclovir in children. Intraocular ganciclovir implants are effective in adults with HIV and CMV retinitis,\textsuperscript{94} but have not been studied in children.

For induction therapy in children we recommend:

\textbf{ganciclovir 5 mg/kg IV, 12-hourly for 14–21 days}

For adolescents, we recommend:

\textbf{valganciclovir 900 mg orally, 12-hourly for 14 to 21 days}

For maintenance therapy, we recommend specialist advice.

\textbf{Toxoplasma chorioretinitis}

\textit{Toxoplasma gondii} is an ubiquitous human parasite that can be ingested in undercooked meat or in contaminated soil or water. Infection of the retina results in acute intraocular inflammation (chorioretinitis) and the formation of a retinal scar. Congenital toxoplasmosis has an incidence of 1 in 1000 to 1 in 10,000 and is an important cause of chorioretinitis. Chorioretinitis can recur at any time, often years after the first infection. The mechanism of damage may be infectious due to the local release of \textit{T. gondii} parasites from cysts in the retina or inflammatory due to an immune response to retinal antigens normally hidden from immune surveillance and released due to cyst reactivation.\textsuperscript{95} Chorioretinitis can also result from post-natally acquired toxoplasmosis, which is at least as common as chorioretinitis from congenital infection.\textsuperscript{96} The diagnosis of toxoplasma infection is usually made clinically by the ophthalmologist, on the basis of a classic raised chorioretinitis with pigmentation.

There is good evidence in favor of treating congenital toxoplasmosis, including babies with toxoplasma chorioretinitis, which will not be covered here.

A Cochrane review of antibiotic therapy for toxoplasma chorioretinitis found three eligible trials, all methodologically poor, which randomized a total of 173 participants.\textsuperscript{97} The authors concluded that there is a lack of evidence to support routine antibiotic treatment for acute toxoplasma chorioretinitis, although weak evidence to suggest that long-term treatment of patients with chronic recurrent toxoplasma chorioretinitis may reduce the risk of recurrence.\textsuperscript{97} Nevertheless, based on accumulated experience, most uveitis specialists agree that treatment of acute toxoplasma chorioretinitis is warranted, although there is no consensus regarding the best treatment regimen.\textsuperscript{98}

An RCT found that 6 weeks treatment for acute toxoplasma chorioretinitis with trimethoprim-sulfamethoxazole was virtually identical to pyrimethamine and sulfadiazine in terms of resolution and adverse reactions.\textsuperscript{99}

Possible regimens, to be continued for 6 weeks, are:

\begin{itemize}
  \item \textbf{trimethoprim+sulfamethoxazole 4 + 20 mg/kg (max 160 + 800 mg) orally 12-hourly OR}
  \item \textbf{pyrimethamine 2.5 mg/kg (max 100 mg) orally, once daily for 2 days, followed by 1 mg/kg (max 25 mg) orally, daily, for a total of 6 weeks PLUS EITHER}
  \item \textbf{sulfadiazine 50 mg/kg (max 1.5 g) orally, 6-hourly OR}
  \item \textbf{clindamycin 10 mg/kg (max 450 mg) orally, 8-hourly}
\end{itemize}

[*Patients on long-term pyrimethamine need to be given daily folate or folic acid supplements (adult dose 5 mg).]

Adjunctive corticosteroid therapy is often used to reduce the duration and severity of acute symptoms due to intraocular inflammation, but there are no RCTs of their use. It is recommended that they not be given without concomitant antimicrobials, because of anecdotal reports of fulminant infection.\textsuperscript{100}

\textbf{References}

26 Sheikh A, Hurwitz B. Antibiotics versus placebo for acute bacterial conjunctivitis. The Cochrane Database of Systematic Reviews 2006(2);Art No CD001211.
83 Endophthalmitis Vitrectomy Study Group. Results of the Endophthalmitis Vitrectomy Study. A randomized trial of immediate vitrectomy and of intravenous antibiotics for the
CHAPTER 6
Fever

Fever is a common symptom in childhood, usually but not always indicating an infection. The physician or pediatrician assessing a febrile child needs to consider some important questions:

1. Is it likely this child has a viral infection, and if so, is it safe to watch the child at home?
2. Does this child have a bacterial infection that can be treated with oral antibiotics at home?
3. Does this child need hospital admission for observation and/or antibiotics?
4. Does this child have a non-bacterial, treatable cause of fever, such as Kawasaki disease?
5. Does this child have life-threatening bacterial infection, so that I need to give the child immediate antibiotic treatment?

Assessment of the febrile child can be greatly assisted by clinical and epidemiologic considerations, which in themselves help predict the likelihood that any particular child has a serious bacterial infection (SBI).

Key factors in the assessment are:
- the child’s age;
- height of temperature;
- presence or absence of a focus of infection;
- presence or absence of “toxicity.”

6.1 What constitutes a fever?

This deceptively simple question defies a simple answer. The normal body temperature is subject to diurnal variation, and temperature may vary with age. The measured temperature varies depending on the site of temperature measurement (see below) and physical activity.

A study of 691 apparently well babies aged 0–3 months attending a well baby clinic1 found a mean rectal temperature of 37.5°C, with standard deviation (SD) 0.3°C. Using these data, if a fever is defined as 2 SD above the mean, a baby aged 0–3 months would be defined as febrile if the rectal temperature exceeded 38.1°C.

For older children, the normal rectal temperature is often quoted as 37°C. We found numerous comparisons of temperatures measured in different ways, but no study exclusively of normal children’s temperature.2 The definition of fever employed will determine what is considered “abnormal,” but conventionally children are usually defined as febrile if their core temperature exceeds 38°C, while studies of “highly febrile” children take a cutoff of 39°C, 39.5°C, or even 40°C.

The cutoff used for defining fever will thus determine the characteristics of the febrile children included in any study.

6.2 Measurement of temperature

Question | For determining a child’s temperature, are axillary, tympanic, or oral temperature measurements sensitive and specific compared to rectal temperature measurement?

Literature review | We found three systematic reviews that reviewed different techniques in terms of accuracy3–5 and acceptability.3

It is not possible to measure “core” temperature noninvasively. The best approximation to core temperature is the rectal temperature. There is debate about the optimum way of measuring a child’s temperature, taking into account sensitivity and specificity but also acceptability to the child, the family, and health care professionals. A systematic review of optimal methods of temperature measurement found 33 primary research studies (10 graded as superior and 23 as average quality).3 The following were the conclusions:
- Electronic digital and disposable crystal thermometers were as accurate as mercury glass (2 studies).
- Axillary temperatures were inaccurate, inconsistent, and insensitive in children >1 month (11 studies).
- Infrared tympanic temperatures were inaccurate, inconsistent, and insensitive at all ages (20 studies).
Parents and staff preferred infrared tympanic thermometers for speed, hygiene, and safety (4 studies).

A subsequent systematic review\(^2\) comparing axillary and rectal temperatures found that axillary temperatures were on average 0.17°C lower than rectal temperatures in neonates and 0.92°C lower in older children and “young people.” There was wide variation across studies. The authors concluded that this has implications for clinical situations where temperature needs to be measured with precision.\(^2\)

The same authors performed a systematic review comparing infrared ear thermometry with rectal thermometry.\(^4\) Their conclusion from 22 comparisons involving 2679 children was that the mean difference was smaller than for axillary temperature at 0.29°C, but the confidence intervals were very wide, meaning that ear temperature could not be considered a good approximation of rectal temperature.\(^3\) Although others have argued in favor of infrared thermometry\(^5\) on grounds of acceptability and adequate accuracy, a review suggested that infrared ear thermometry would fail to diagnose fever (>38°C) in 3 or 4 out of every 10 febrile children.\(^6\) This suggests that tympanic membrane measurement is not sufficiently accurate for excluding fever in children.

There is a paucity of data on oral temperature measurement.\(^3\) At present, rectal temperatures represent the "gold standard" in day-to-day clinical practice. If temperature is measured in the axilla or ear, it should be with the knowledge that the axillary temperature is likely to be about 1°C lower than the rectal temperature and that the ear temperature will miss fever in 30–40% of children. We recommend the use of rectal or axillary temperature measurement when it is important to rule in or rule out fever.

### 6.3 Height of fever

**Question** | In a population of febrile children, are children with higher fever more likely than less febrile children to have serious bacterial infection (SBI)?  
**Literature review** | We found 20 papers that examined the relation between height of fever and incidence of bacterial infection. We found a systematic review for infants <3 months old\(^7\) and another for children aged 3–36 months.\(^8\)

In a retrospective study of infants aged 4–8 weeks, the rate of SBI increased in direct proportion to fever height, being 3.2% in those with a temperature 38.1–38.9°C, 5.2% in those with a temperature 39–39.9°C, and 26% in those with a temperature >39.9°C.\(^9\) On the other hand, a systematic review\(^7\) found four other studies that looked at predictors of bacteremia in infants <3 months and included temperature as a variable. None found a relationship between the height of fever and the risk of SBI.\(^7\)

A systematic review of height of temperature in children aged 3–36 months found 14 studies. These showed that the risk of pneumococcal bacteremia, which was the commonest outcome studied, increased with the height of temperature. In the era before pneumococcal immunization, the incidence of pneumococcal bacteremia in children aged 3–36 months increased progressively from 1.2% for temperature <39.5°C to 4.4% for a temperature of 40.5°C or above.\(^8\) In the era before Hib immunization, the height of fever did not correlate with the risk of Hib bacteremia.\(^10\) There are no data correlating height of fever with risk of bacteremia due to other organisms.\(^8\)

### 6.4 Age of the febrile child

#### Febrile neonate

The younger the febrile child, the greater is the incidence of SBI. For febrile neonates the risk of SBI is 12–32%.\(^7,11,12\) Studies have shown that even if neonates are identified as being at relatively low risk using the Rochester criteria (see Section 6.5, p. 57, and Table 6.2), 3–6% of supposedly low-risk neonates would have an SBI and 2% will have bacteremia.\(^7,11,12\) This means it will be necessary to treat 17–33 “low-risk” febrile neonates with empiric parenteral antibiotics to avoid missing one baby with SBI. Because of the high risk that a neonate with SBI will deteriorate, we recommend admitting all febrile neonates, taking appropriate cultures, and starting antibiotics. The antibiotics can be stopped usually after 48 hours if cultures are negative.

**Recommendation:** All febrile neonates (0–28 days) with temperature >38°C should be admitted to hospital and investigated and treated empirically for bacterial infection, until culture results are available.

#### Infant aged 1–3 months

For febrile infants aged 1–3 months, the risk of SBI, in the era before pneumococcal immunization, was about
15–21%6,7,13,14 which is higher than for children aged 3–36 months.8

Is it possible to identify a sub-population of infants aged 1–3 months at low risk for SBI who might be managed as outpatients?

6.5 Clinical assessment of the febrile child

Question | In febrile infants aged 28–90 days, can clinical assessment identify a sub-population of infants at low risk of SBI who might be managed safely as outpatients?

Literature review | We identified 16 studies and 2 systematic reviews15,16 which identified infants at low risk for SBI.

Dagan and colleagues have developed criteria, known as the Rochester criteria, which describe babies <2 months old (60 days) with fever but at low risk for SBI.17,18 The Rochester criteria are shown in Box 6.1.

In one systematic review,15 the likelihood that infants aged 1–3 months, defined as low risk using the Rochester criteria, had SBI was 0.9% and had bacteremia was 0.65%. Using a broader definition of low risk, the authors found that the risk of SBI was 1.4%, of bacteremia was 1.1%, and of meningitis was 0.5%.15

Another systematic review16 of 10 studies concluded that if the Rochester criteria were satisfied, the probability of an infant having SBI was reduced from 7 to 0.2%. In contrast, a more recent review7 estimated that the overall probability of bacteremia for a low-risk febrile infant was 0.8% and of SBI was 2%.

Box 6.1 Rochester criteria for low risk-febrile babies aged <60 days.17,18

- Infant appears well and not toxic
- Previously healthy
- Born at term
- No antenatal or perinatal antibiotics
- Not treated for prolonged jaundice
- Not in hospital longer than the mother after birth
- Not hospitalized sub-sequently
- No recent antibiotics
- No evidence of bacterial infection (skin, soft tissue, bone, joint, ear)

It is arguable whether or not these data support management of low-risk infants as outpatients. In the era prior to immunization with pneumococcal conjugate vaccine, it was common practice to give low-risk infants and children a dose of IM ceftriaxone and to send them home. This practice is less common and less justifiable in places where universal pneumococcal immunization has resulted in pneumococcal bacteremia being extremely rare; in a recent US study the rate was 0.2% of febrile children aged 3–36 months.19

In our algorithm shown in Figure 6.1, we suggest that all febrile children aged <3 months at high risk for SBI (see Box 6.1 for low-risk criteria) should be admitted to hospital for empiric antibiotic treatment. An alternative that avoids hospital admission is to identify babies at low risk for SBI using the Rochester criteria, take cultures, give an IM or IV dose of a long-acting antibiotic such as ceftriaxone, and review the next day.

Toxicity

Question | In children with fever, can clinical examination predict reliably which babies have sepsis?

Literature review | We found 4 studies and 1 systematic review7 in babies <3 months old and 19 studies and 1 review8 in children 3–36 months old.

Pediatricians often use a term, “toxicity,” or talk about a “toxic child,” to describe febrile children who are non-specifically unwell, based on assessment of the child’s level of activity, responsiveness, feeding, and peripheral perfusion. The sensitivity of an assessment that an infant <3 months old was toxic varied from 11 to 100% in four studies.7 This variation may reflect the experience of the clinicians and thus be measuring their clinical acumen. Various researchers have attempted to define and quantify the signs and symptoms for clinical scoring systems to predict the likelihood of serious infection. The Yale Observation Score,20 the Young Infant Observation Scale,21 and a Melbourne scoring system22 have all been evaluated. Studies have shown that febrile children who are judged as being toxic are more likely to have SBI, there are problems. Large prospective studies show that scoring systems identify only 33–76% of infants <3 months old with SBI.7 For older children, clinical scoring systems are even less sensitive,8 and there is a group of children with high fever and so-called occult bacteremia who are not judged as being
Figure 6.1 Algorithm for management of the febrile child <3 years old. In a population fully immunized with pneumococcal conjugate vaccine, it may not be necessary to measure WBC and serum CRP, but to review these children after 12–24 hours. (Modified from Reference 36.)

toxic by any criteria. Most of these children had occult pneumococcal bacteremia.

If a young febrile child <36 months old is judged as toxic, the risk of their having SBI is increased to the extent that it would seem wise to admit them to hospital for empiric antibiotics, pending the results of cultures. The signs of toxicity described in the infant observation scales are one or more of the following: decreased alertness and arousal, altered breathing, blue lips, cold peripheries, weak, high-pitched cry, and decreased fluid intake and/or urine output. These signs are summarized in Box 6.2.
Box 6.2 Signs of toxicity in febrile young children aged 0–36 months.20–22

Toxicity: ABCD
The signs of toxicity in infants are:
A = arousal, alertness, and activity (decreased in a toxic child)
B = breathing difficulties (tachypnea or labored breathing)
C = color (pale) and/or circulation (cold peripheries) and/or cry (weak, high pitched)
D = decreased fluid intake (< half normal) and decreased urine output (<4 wet nappies a day)
- Abnormality of any of these signs places the child at increased risk of serious illness
- The presence of more than one sign increases the risk
- The toxic child may appear drowsy, lethargic or irritable, pale, mottled, and tachycardic

Focus of infection
If there is a clinically apparent focus of infection, this will direct investigations and specific therapy and also alters the likelihood of bacteremia. For example, a child with a high fever who has acute otitis media or acute tonsillopharyngitis is less likely to be bacteremic than a child with no focus of infection.8 Some children with a focus can be treated with oral antibiotics without further investigation and sent home, e.g., acute otitis media (see Chapter 12). A child who is toxic should be assessed carefully, even if there is a focus of infection, because a child with acute otitis media, for example, may also have systemic sepsis.

6.6 Investigation of febrile child
Not all febrile children need investigations. Indeed, most febrile children are diagnosed as having presumed viral infection and managed safely in the community. The decision as to whether or not to investigate should be made on the basis of an estimate of the risk that the child has SBI. This in turn depends on the criteria already described: age, height of fever, signs of toxicity, and focus of infection.

White blood count
The peripheral blood white blood cell count (WBC) is a relatively poor predictor of SBI in young infants <3 months old. A review7 found that the sensitivity of a total WBC > 15,000/mm³ (15 × 10⁹/L) for SBI was only 31–52% and the specificity 77–96%, although the absolute band count had a better sensitivity of 86–88%. The total WBC is a better predictor of SBI in children aged 3–36 months because most children with pneumococcal infection have a high WBC and, before immunization against Streptococcus pneumoniae, pneumococcal infections far outweighed other causes of bacteremia.8

In one preimmunization study, 86% of children with pneumococcal bacteremia had a WBC > 15,000/mm³ (sensitivity 86%), but 23% of non-bacteremic children also had a WBC > 15,000/mm³ (specificity 77%).23 In such a population, the WBC can be used to screen highly febrile children with no focus of infection. If the incidence of pneumococcal bacteremia in a population of children aged 3–36 months with fever > 39°C and no focus is 4%,8 then 40 out of every 1000 highly febrile children will have pneumococcal bacteremia, of whom 34 will have a WBC > 15,000/mm³, while 96 will not have bacteremia, but 220 will have a WBC > 15. If a cutoff of 20,000/mm³ is used, then fewer children without bacteremia will be treated, but at the cost of missing more children with pneumococcal bacteremia.24 The cutoff used determines how many uninfected children are investigated and treated to avoid missing an infected child.

Universal infant immunization with 7-valent pneumococcal conjugate vaccine was introduced in the USA in 2000. Since then, a Kaiser Permanente study19 found that the incidence of pneumococcal bacteremia in febrile children aged 3–36 months had fallen from 1.3 to 0.2% and the overall incidence of bacteremia from 1.6 to 0.7%. In this population, the sensitivity of a WBC > 15,000/mm³ was 74% and the specificity 54.5%, which means that the peripheral blood white cell count is a relatively poor predictor of bacteremia in 3–36-month-old children from a population immunized against pneumococcus, only identifying three of four children with bacteremia.

Acute phase reactants
Serum C-reactive protein (CRP) is the most widely used and best studied of the acute phase reactants.25–31 It is superior to the WBC as a predictor of occult SBI. In one study, a serum CRP > 7 mg/dL had a sensitivity of 79% and a specificity of 91% for predicting occult SBI and a higher likelihood ratio than WCC or
absolute neutrophil count. However, these data are from the days before universal pneumococcal immunization, and as for WBC, post-pneumococcal immunization studies may show that there are so few children with occult SBI that using an abnormal serum CRP may lead to treating many children to benefit none or very few.

Other acute phase reactants that are promising but less readily available include serum procalcitonin, IL-6, IL-8, and IL-1 receptor antagonist.

No test has 100% sensitivity for predicting the febrile child with SBI. The use of serum CRP can help identify those children at risk of occult SBI who would benefit from hospitalization and/or systemic antibiotics. The cutoff point for an abnormal CRP can be set to try to obtain the best balance between over- and undertreatment.

**Urinalysis and urine culture**
Urinary tract infection is the commonest SBI in a febrile child with no clinically apparent focus of infection. A completely normal urinalysis makes urinary tract infection extremely unlikely (see Chapter 17), although if there is no focus, urine should be sent for culture. Bag urines should not be used for culture when starting empiric antibiotics because of the high risk of contaminated urine. It is not necessary to send urine for culture if there is another focus, e.g., the child has a respiratory infection, and especially if the urinalysis is also normal.

**Cerebrospinal fluid (CSF)**
The need for CSF examination depends on the incidence of meningitis, which in turn depends on the age, immunization status (Hib, pneumococcal, meningococcal), and on the clinical examination (see Section 10.1, p. 132). In general, the younger the child, the less reliable is the clinical examination in excluding meningitis and so lower the threshold recommended to perform a lumbar puncture (LP). The arguments for deferring LP in a very sick child are discussed in Chapter 10 (see p. 133 and Table 10.1).

**Chest radiograph**
Febrile children without respiratory symptoms often have a chest radiograph performed to exclude pneumonia. A systematic review of three observational studies concluded that there is level II evidence that the yield is so low that chest X-ray is not indicated in a febrile child aged <2 years with no respiratory signs or symptoms. One study of febrile children aged 3 months to 15 years found that none of 41 without chest signs had an abnormal chest X-ray. In contrast, 5 of 173 febrile infants aged <3 months without respiratory distress had abnormal chest X-rays. If an abnormal chest X-ray would change practice, in terms of initiating or continuing antibiotics, then it may be indicated in febrile infants <3 months old even in the absence of chest signs.

### 6.7 Management of the febrile child
An algorithm developed for the management of the febrile child in the era before universal infant pneumococcal immunization, and modified to include serum CRP measurement, is shown in Figure 6.1. We strongly recommend admitting all febrile neonates and treating them with empiric antibiotics. We have recommended also admitting and treating all febrile infants aged 1–3 months, although we acknowledge that it would be reasonable to use the Rochester criteria to identify low-risk infants aged 1–3 months and to manage them as outpatients with or without antibiotics. The data are not yet sufficient to confirm whether or not, in the pneumococcal vaccine era, it is safe to omit measurement of serum CRP and WBC in the well-looking child aged 3–36 months with fever > 39°C but no focus of infection.

**Antibiotics**
The choice of empiric antibiotics for treating a febrile child will depend on the severity of the illness, on the child’s and the population’s immunization status, and on the epidemiology of local organisms causing sepsis. If the child is severely unwell, see Chapter 15. For the febrile child with no focus of infection, who is well or moderately unwell, has a normal urinalysis, does not have meningitis (normal CSF or old enough for meningitis to be excluded clinically), and for whom antibiotics are indicated, for example, in the algorithm in Figure 6.1, we recommend:

- 0–3 months old: amoxi/ampicillin 50 mg/kg IV, 6-hourly PLUS gentamicin 7.5 mg/kg IV, daily
- 4 months to 4 years: benzylpenicillin 30 mg (50,000 U)/kg IV, 6-hourly OR
Ceftriaxone 50 mg/kg IV or IM, daily OR
Over 4 years: THE COMBINATION OF benzylpenicillin 30 mg (50,000 U)/kg (max 1.2 g or 2 million U) IV, 6-hourly PLUS di/fluc/oxa/naclillin 50 mg/kg (max 2 g) IV, 6-hourly OR, AS A SINGLE AGENT cefotaxime 50 mg/kg IV, 8-hourly OR ceftriaxone 50 mg/kg IV or IM, daily

These recommendations are not based on RCTs, but on epidemiologic data on the likely organisms causing infection in industrialized countries.

In babies 0–3 months old, it is necessary to cover for group B streptococcus, meningococcus, Listeria, and Gram-negative enteric bacilli, among other organisms.

For children aged 4 months to 4 years with a normal urinalysis, meningococcus and pneumococcus are the major pathogens in industrialized countries, while Staphylococcus aureus should also be considered in older children. Benzylpenicillin is acceptable provided meningitis has been excluded and the child is immunized against Hib.

Ceftriaxone 50 mg/kg IM as a daily dose has been widely recommended and often used, especially when hospitalization is not an option or is not preferred. Ceftriaxone is inactive against Listeria (which is a rare cause of sepsis aged 1–3 months) and has relatively poor activity against S. aureus. These organisms are exceedingly rare in children aged 4 months to 4 years, and IM ceftriaxone is an option for these children. The main disadvantage of giving IM ceftriaxone to children who are being sent home is that the number of children you need to treat to prevent one case of septicemia or meningitis is high (several hundred) and will rise in countries which use universal pneumococcal immunization, and studies have shown that a population of older infants and children can be safely managed as outpatients.

Antipyretics
Antipyretics may be given to reduce fever or to reduce symptoms such as irritability. The most frequently used antipyretics are acetaminophen (which is the same as paracetamol) and ibuprofen.

Question | For febrile children, do antipyretics compared with placebo or other antipyretics reduce fever and irritability?

Literature review | We found 35 RCTs, 2 systematic reviews, and a Cochrane review.

A Cochrane review found only 12 trials that compared the antipyretic effects of paracetamol with placebo or physical methods, and could find no evidence that paracetamol was effective in reducing the overall duration of fever. Although paracetamol did not reduce the duration of fever in one study, children treated with paracetamol were more active and alert, but had no detectable improvement in mood, comfort, appetite, or fluid intake.

A systematic review of 22 articles comparing acetaminophen with ibuprofen found that acetaminophen produced a greater body temperature reduction than ibuprofen 30 minutes after administration. However, ibuprofen provided a longer duration of antipyretic effect than acetaminophen, and the initial temperature decrement lasted longer. A systematic review examined the effect of ibuprofen and acetaminophen on pain and fever in children. Single doses of ibuprofen (4–10 mg/kg) and acetaminophen (7–15 mg/kg) were comparable to analgesics or antipyretics in terms of efficacy and safety for relieving moderate to severe pain. Ibuprofen (5–10 mg/kg) was a more effective antipyretic than acetaminophen (10–15 mg/kg) at 2, 4, and 6 hours post-treatment.

Although there are anecdotal reports of liver toxicity and even hepatic failure with acetaminophen/paracetamol given for fever, such events are rare and usually relate to inadvertent overdose due to persistent administration at high doses, compounded in some cases by infection with a virus that might cause hepatitis. Ibuprofen can be associated with gastrointestinal bleeding, anaphylaxis, and renal failure in adults, although rarely in children. In a study of over 27,000 children randomized to acetaminophen or ibuprofen, 3 children, all in the ibuprofen group, were hospitalized with gastrointestinal bleeding (rate 17 per 100,000 for ibuprofen, not statistically significantly raised). There were no other adverse reactions.
Two studies suggested that alternating doses of acetaminophen (paracetamol) with doses of ibuprofen on a 4-hourly basis had a greater antipyretic effect than monotherapy with either alone.\textsuperscript{43,44} An Israeli study of 464 infants in day care found that the alternating regimen, given for 3 days, was associated with less fever but also with less stress and less absenteeism from day care.\textsuperscript{44} While these results are interesting, they are preliminary, and it is unclear whether or not using alternating medications would be confusing and would increase the risk of toxicity. An emergency department-based study found that giving acetaminophen and ibuprofen simultaneously reduced the temperature by less than 0.5°C compared with monotherapy; the authors considered this change insufficient to warrant routine use.\textsuperscript{45}

**Question** | In children with fever, is the response to antipyretics able to distinguish children with bacterial infection from children with viral infection?

**Literature review** | We found four prospective studies\textsuperscript{46–49} and a review.\textsuperscript{7}

Children with viral infections respond the same as those with bacterial infection to antipyretics.\textsuperscript{7,46–49} It is not possible to differentiate bacterial from viral infection by the response to antipyretics.

**Physical methods for reducing fever**

A Cochrane review\textsuperscript{50} found seven studies (467 children) comparing temperature reduction by physical methods such as tepid sponging with medication or placebo. Tepid sponging had an additive effect on reducing fever when used with an antipyretic. The only adverse effects were shivering and goose pimples.

We give our recommendations on the use of antipyretics and physical methods for managing fever in febrile children in Box 6.3.

### Box 6.3 Recommendations on managing fever in children.

- Use antipyretics only if necessary for comfort (child’s or parents’)
- Try physical methods first, such as tepid sponging
- The recommended dose of acetaminophen/paracetamol is 15 mg/kg (max 600 mg), orally, no more than every 4 h, to a maximum of 4 doses/day (max 2.4 g/day)
- It is not recommended to give acetaminophen/paracetamol for more than 3 days without seeking medical advice
- The recommended dose of ibuprofen is 5–10 mg/kg (max 400 mg), orally, given 6–8-hourly, to a maximum of 4 doses/day
- Ibuprofen is not recommended for babies < 6 mo old

We found five case series of children presenting to hospital with fever and petechial rash, all from industrialized countries.\textsuperscript{51–55} The incidence of SBI was much lower in the largest study, from Boston Children’s Hospital.\textsuperscript{53} The results are summarized in Table 6.1.

In one paper from the USA pre-Hib vaccines, Hib caused 6.2% of cases.\textsuperscript{51} In another US study, group A streptococcus was responsible for 10% of cases and viral infections for 14.7%.\textsuperscript{52} In the study from Denmark, enterovirus was found in 7% and adenovirus in 4% of cases.\textsuperscript{55}

Other causes of fever and petechiae described in these papers, and in case reports and case series, included children with infections with \textit{S. pneumoniae},\textsuperscript{57} \textit{S. aureus}, rickettsial infections including Rocky Mountain spotted fever in North America and Q fever, various viral infections including influenza A, and endocarditis.

In a UK case series of 233 children presenting with non-blanching rash,\textsuperscript{56} 26 (11%) had meningococcal disease at a time of relatively high UK incidence of meningococcal infection. Children with meningococcal infection were more likely than children without meningococcal to be assessed as “ill” (not otherwise defined), to be pyrexic (> 38.5°C), have purpura, and a capillary refill time < 2 seconds. Five of 26 children with meningococcal disease (19.2%) had an axillary temperature below 37.5°C. No child with a rash confined to the distribution of the superior vena cava had meningococcal infection. Investigations were less helpful, although

### 6.8 Fever and petechial rash or purpura

**Question** | When a child presents with fever and petechiae (non-blanching rash), what is the likelihood of meningococcal infection and what of other severe bacterial infections?

**Literature review** | We found five observational studies (case series) of the incidence of SBI in children presenting with petechiae and fever\textsuperscript{51–55} and one case series of non-blanching rash.\textsuperscript{56}
Table 6.1 Published case series of children with fever and petechial rash.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country of Study</th>
<th>Number of Children</th>
<th>All SBIs</th>
<th>Meningococcal Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Nguyen, 1984(^{51})</td>
<td>USA</td>
<td>129</td>
<td>26 (20.2%)</td>
<td>13 (11.1%)</td>
</tr>
<tr>
<td>Baker, 1989(^{52})</td>
<td>USA</td>
<td>190</td>
<td>32 (16.8%)</td>
<td>13 (6.8%)</td>
</tr>
<tr>
<td>Mandl, 1997(^{53})</td>
<td>USA</td>
<td>411</td>
<td>6 (1.5%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>Brogan, 2000(^{54})</td>
<td>UK</td>
<td>55</td>
<td>5 (9.9%)</td>
<td>3 (5.5%)</td>
</tr>
<tr>
<td>Nielsen, 2001(^{55})</td>
<td>Denmark</td>
<td>264</td>
<td>45 (17.0%)</td>
<td>40 (15.2%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>1049</strong></td>
<td><strong>104 (10.0%)</strong></td>
<td><strong>73 (7.0%)</strong></td>
</tr>
</tbody>
</table>

children with meningococcal infection were more likely to have an abnormal neutrophil count and a prolonged international normalized ratio. No child with a serum CRP <6 mg/L had meningococcal infection.\(^{56}\)

Most primary care physicians will never see a child with meningococcal infection in their practice and may or may not have seen infected children during their hospital training. In industrialized countries, about 7% of children presenting to hospital with fever and petechiae have meningococcal infection with a range from 0.5 to 15%.\(^{51-53}\) Hospital-based series are subject to selection bias. Presumably, children presenting to general practitioners and pediatricians outside hospital with fever and petechial rash are less likely to have meningococcal infection and more likely to have viral infections, although we could not find any case series of the causes of fever and rash in children presenting outside hospital. Children with meningococcal infection are more likely to look ill and have poor perfusion (assessed by capillary refill time), but in one study as many as 19% were afebrile.\(^{56}\)

Not all children with meningococcal infection have a petechial rash at presentation. In one large case series of 448 children with meningococcal infection, a petechial rash was present in 42% of children <1 year old and 65–70% of older children and adolescents.\(^{58}\)

The primary care physician and the pediatrician need to decide:

- which children with petechiae and fever need admission to hospital;
- how to identify children with meningococcal infection as early as possible.

The decision on which child with fever and petechiae needs hospital admission will depend on local circumstances, such as the incidence of meningococcal infection, on the experience of the clinician, and on the history and examination, in particular whether the child is well or “toxic” (see below). A survey found substantial differences among North American pediatricians when asked how they would investigate and treat a child with fever and petechial rash who did not appear toxic, with community-based and academic general pediatricians less likely to take blood cultures and admit children to hospital than pediatricians specializing in emergency medicine and infectious diseases.\(^{59}\)

We will discuss in detail the presentation and clinical management of a child with suspected meningococcal infection in Chapter 15.

### 6.9 Kawasaki disease (KD)

KD is an acute, self-limited systemic vasculitis, of unknown etiology, which if untreated can lead to coronary artery aneurysms in 25% of cases.\(^{50-53}\) There is as yet no diagnostic test for KD. Diagnostic criteria have been developed for KD (see Box 6.4). It should be emphasized that these are epidemiologic criteria that were developed more to allow epidemiologic comparisons than to decide which children with KD should be treated.

Some children will not have all the classic diagnostic features of KD, but will nevertheless start to develop coronary artery dilatation and aneurysm formation. Such children are said to have incomplete or atypical KD, and recommendations for the evaluation of children with suspected incomplete KD have been published.\(^{60}\)

**Laboratory tests for KD**

Laboratory investigations that can help with the diagnosis of KD are given in Box 6.5. It should be pointed out that only 50–60% of children with KD have a WBC
Box 6.4 Diagnostic criteria for Kawasaki disease.

Fever for 5 or more days
AND
Presence of at least four of:
1 bilateral bulbar conjunctival injection without exudate
2 polymorphous rash
3 oral changes: red, dry, cracked lips, strawberry tongue, oropharyngeal erythema
4 changes in extremities: erythema and/or edema of palms and soles, desquamation
5 cervical lymphadenopathy
AND
Exclusion of other diseases, e.g., measles, group A streptococcal infection, and viral infections
OR
Child with fewer features but who develops coronary artery aneurysms

>15,000/mm³, that 70–90% have raised ESR and/or CRP, that thrombocytosis is unusual at the time of diagnosis, and that abnormalities of liver enzymes and serum albumin are present in less than 50% of children with KD.⁶⁰,⁶¹ Thus, although laboratory tests can be supportive, KD is primarily a clinical diagnosis and the decision to treat is a clinical one.

Echocardiography in KD
The echocardiogram should not be used as a diagnostic test for KD, and the decision whether or not to start treatment of KD should not depend solely on the echocardiogram findings. Coronary lesions often develop in the convalescent phase, so a normal echocardiogram does not exclude KD. Indeed, the aim of treatment is to prevent the development of coronary lesions.

Treatment should not be delayed pending an echocardiogram. This is of particular relevance in rural areas where there may be delay in obtaining an echocardiogram. Ideally, however, an echocardiogram should be performed in all patients at or soon after the time of diagnosis, and repeated after 2 and after 6–8 weeks to exclude new lesions, which may rarely develop.⁶⁰,⁶¹ If coronary lesions are present, more frequent review will be necessary.⁶⁰,⁶¹

Management of KD
In reviewing the management of KD, we found 52 guidelines, of which 4 were current and described as evidence-based.⁶⁰–⁶³

Intravenous immunoglobulin (IVIG)

Question | For children with KD, do IVIGs compared with placebo or no IVIG reduce the incidence of coronary artery abnormalities (CAAs)?

Literature review | We found 16 RCTs and a Cochrane review.⁶⁴

The mainstay of the treatment of KD is the use of IVIG. The mechanism of action is uncertain, but there is no doubt about the efficacy of IVIG. A Cochrane meta-analysis of 16 trials of IVIG versus placebo⁶⁴ showed a significant decrease in new CAAs in favor of IVIG at 30 days $RR = 0.74$ (95% CI 0.61–0.90). No statistically significant difference was found thereafter. A sub-group analysis excluding children with CAAs at enrolment also found a reduction of new CAAs in children receiving IVIG: $RR = 0.67$ (95% CI 0.46–1.00).⁶⁴

Results of dose comparisons showed the number of new CAAs decreased with increased dose. A single dose of 2 g/kg was superior to 400 mg/kg/day for 5 days and showed a statistically significant reduction in CAAs at 30 days ($RR = 0.22$, 95% CI 0.08–0.65). This comparison also showed a significant reduction in duration of fever with the higher dose.⁶⁴

There was no statistically significant difference noted between different preparations of IVIG.

The authors concluded that children fulfilling the diagnostic criteria for KD should be treated with IVIG (2 g/kg single dose) within 10 days of onset of symptoms.⁶⁴

Box 6.5 Helpful investigations in suspected Kawasaki disease.

Neutrophil leukocytosis: present in the majority of patients, often with toxic changes
Platelet count: thrombocytosis common, but only from second week of illness
Inflammation: raised ESR and serum CRP usual
Liver transaminases raised in up to 40% of patients
Aspirin

**Question** | In children with KD, does high-dose aspirin therapy compared with no aspirin or low-dose aspirin or placebo reduce the incidence of CAA?

**Literature review** | We found no studies comparing aspirin with placebo. We found six poor-quality comparative studies. We found a Cochrane review\(^6\text{5}\) and two non-Cochrane meta-analyses.\(^6\text{6,67}\)

Before IVIG was studied, aspirin was the mainstay of the treatment of KD. It has never been subjected to a satisfactory RCT. The rationale for aspirin use is either as an anti-inflammatory, when high doses would be better than low, or as an antithrombotic agent, when low dose would be preferred.

The Cochrane review\(^6\text{5}\) found only one study involving 102 children which was described as randomized, but it was not possible to confirm the method of treatment allocation.\(^6\text{8}\) The paper compared aspirin alone (30–50 mg/kg/day until defervescence) with aspirin plus IVIG with IVIG alone. The incidence of coronary artery aneurysms was reported as 39–42\% with aspirin but 14–21\% with IVIG.\(^6\text{8}\) A non-Cochrane meta-analysis\(^6\text{6}\) and a subsequent retrospective study\(^6\text{9}\) found no difference in the incidence of coronary artery aneurysms at 30 or 60 days between patients who received high-dose IVIG plus low-dose aspirin (80 mg/kg/day or less) and those who received high-dose IVIG with high-dose aspirin (>80 mg/kg/day). A second non-Cochrane meta-analysis of the role of IVIG and aspirin in KD\(^6\text{7}\) found the incidence of CAAs was inversely related to dose of IVIG, but independent of dose of aspirin. A paper in which children with KD were not given IVIG compared high-dose aspirin (100 mg/kg/day) with low-dose aspirin (30 mg/kg/day).\(^7\text{0}\) There was no difference in the rate of coronary aneurysms (17\% versus 23\%), but the high-dose group developed abnormal liver enzymes. However, the duration of aspirin treatment was longer than is usual.

Finally, a recent study has queried the need for high-dose aspirin. Children diagnosed with KD were given IVIG 2 g/kg but no aspirin initially and 94.4\% defervesced within 3 days.\(^7\text{1}\) The authors concluded that aspirin was unnecessary, but because the study was uncontrolled and there was no aspirin group, it is unsure whether this conclusion is correct.

The current US guidelines\(^6\text{0}\) are to use aspirin 80–100 mg/kg/day in four divided doses during the acute phase of the illness, while the Australian,\(^6\text{1}\) UK,\(^6\text{2}\) and Japanese\(^6\text{3}\) recommendations are for 30–50 mg/kg/day in three divided doses, to reduce gastrointestinal adverse events.

All authorities\(^6\text{0–63}\) recommend that as soon as the child defervesces, the dose of aspirin should be dropped to an antithrombotic dose of 3–5 mg/kg once daily. This should be continued, even if the initial echocardiogram is normal, until the follow-up echocardiogram at 6–8 weeks shows no CAA.

We feel that the evidence for using high-dose aspirin in the initial phase of acute KD is weak and that it would be perfectly reasonable to treat with IVIG and only to add high-dose aspirin for children who failed to defervesce. There is no evidence that low-dose aspirin decreases the risk of thrombosis, but this is a relatively benign treatment so that the risks and cost are minimal.

Corticosteroids

**Question** | In children with KD, do corticosteroids compared with no corticosteroids or placebo improve outcome in KD?

**Literature review** | We found 10 studies of the use of corticosteroids and a meta-analysis\(^7\text{2}\) but only 1 RCT.\(^7\text{3}\)

Corticosteroids were often used in Japan in the early stages of KD treatment. Initial comparisons suggested that corticosteroid-treated children fared worse than children who did not receive corticosteroids. However, the studies were retrospective, non-randomized, and highly subject to confounding by selection bias because the corticosteroid-treated children were almost certainly more severely affected.

There has only been one RCT\(^7\text{3}\) that compared 21 children given 2 g/kg IVIG plus aspirin with 18 children given 2 g/kg IVIG plus aspirin plus a single dose of 30 mg/kg pulsed IV methylprednisolone. The steroid-treated children had significantly shorter mean duration of fever (1 day versus 2.4 days), shorter mean hospital stay (1.9 days versus 3.3 days), and lower serum acute phase reactants at 6 weeks. There were no differences in coronary artery size.

A meta-analysis\(^7\text{2}\) of eight studies, of which only one was an RCT, found that corticosteroids, when used in addition to IVIG and aspirin, were associated with
a significant reduction in the incidence of coronary artery aneurysms: RR 0.55 (95% CI 0.37–0.80). The data are based on weak studies and have not convinced any authorities to recommend corticosteroids for primary therapy yet. Larger trials are awaited.

Treatments of acute KD should be started as soon as possible after the onset of fever and within 10 days whenever possible.

Recommendation for initial treatment of acute KD:

**IVIG 2 g/kg, infused over 8–12 hours**
**WITH OR WITHOUT**
**aspirin 30–100 mg/kg orally, 6–8-hourly**

[*Whether or not high-dose aspirin is given initially, we recommend starting or changing to aspirin 3–5 mg/kg orally, daily when the child’s fever has resolved.*]

About 90–95% of children will respond to this regime with immediate resolution of fever within 36 hours.60,71

The above treatment is not indicated if the diagnosis of KD is made retrospectively, e.g., a child who presents with peeling fingers after >2 weeks but who no longer has signs or symptoms of inflammation.

**Children with KD resistant to initial treatment**

About 5–10% of children diagnosed with KD will have fever and signs of inflammation persisting for >36 hours despite IVIG.60,71 The possibility of alternate diagnoses should be reconsidered. If the diagnosis of KD seems highly likely, and particularly if the child has coronary artery dilatation, further treatment is indicated.

The children with KD least likely to respond to initial IVIG are also the children most likely to develop coronary artery aneurysms. Risk factors for coronary artery aneurysms include being <1 year old, male, and a biphasic illness with recurrence of fever after initial defervescence.61–63,74

There are no good trial data to guide the best treatment for children with persistent KD. Most authorities recommend giving a second dose of IVIG 2 g/kg if fever persists after 48 hours. This was followed by defervescence in 9 of 13 children (69%) in one study, while two more of the 13 resolved after a third dose.75 Some workers have used 1 g/kg of IVIG for the second dose, but the scanty data suggest that 2 g/kg may be more effective than 1 g/kg, which resulted in resolution in 18 of 35 children (51%) in one study.76

Corticosteroids have been advocated by some for persistent KD. One small RCT76 randomized 17 patients who had failed to respond to a second dose of IVIG to receive a third dose of IVIG 1 g/kg (8 patients) or 20 mg/kg of methylprednisolone (9 patients). Fever resolved more quickly with corticosteroids (1.4 versus 4.8 days), but perhaps because of low numbers, there was no difference in the incidence of coronary artery aneurysms.

For persistent or recurrent fever after 48 hours, we recommend:

**IVIG 2 g/kg infused over 8–12 hours PLUS**
**aspirin 80–100 mg/kg orally, 6-hourly**

If fever continues despite two doses of IVIG 2 g/kg, we recommend:

**methylprednisolone 30 mg/kg IV infusion over 2–3 hours for 1–3 days**

The evidence for these recommendations is not strong, as already indicated, but they represent our best interpretation of the literature.

### 6.10 Cat scratch disease

Cat scratch disease is caused by infection with *Bartonella henselae*.77 *Bartonella* species cause a variety of clinical syndromes in both immunocompetent and immunocompromised hosts. Domestic cats are the natural reservoir and vectors of *B. henselae*. Infection follows a scratch or lick from an infected cat, usually a kitten or sick cat.77 Asymptomatic *B. henselae* infection is common in early childhood.77 Cat scratch disease typically produces fever and local lymphadenitis. Mild cases resolve spontaneously, but persistent lymphadenitis may require antibiotics and possibly drainage. Other manifestations of cat scratch disease include granulomatous conjunctivitis with ipsilateral preauricular or sub-mandibular lymphadenopathy (Parinaud ocucloglandular syndrome), encephalitis without CSF pleocytosis, endocarditis, hepatitis, osteomyelitis, and fever of unknown origin.77,78

If tissue is not available, the diagnosis of cat scratch disease is made serologically using immunofluorescent assays79 or ELISA,80 both of which have reasonable
sensitivity and specificity. If tissue is available, culture is feasible but PCR is the diagnostic test of choice.\textsuperscript{81}

There are no comparative studies of different antibiotics to treat cat scratch disease. Margileth\textsuperscript{82} retrospectively reviewed 268 patients with cat scratch disease, measuring outcome by clinical improvement in inflammatory and constitutional symptoms, reduced or resolved lymphadenopathy, and falling ESR. Only 4 of 18 different antimicrobials had apparent demonstrable efficacy: rifampicin in 87\% of patients, ciprofloxacin 84\%, gentamicin 73\%, and trimethoprim-sulfamethoxazole in 58\%, but none was compared to placebo.\textsuperscript{82} Penicillins, cephalosporins, tetracycline, and erythromycin had minimal or no apparent clinical efficacy.

There is only a single-randomized, double-blind, placebo-controlled study of any antibiotic in cat scratch disease, azithromycin.\textsuperscript{83} Patients with lymphadenopathy caused by \textit{B. henselae} received either azithromycin or placebo. Affected lymph nodes reduced in size more quickly in azithromycin recipients, but there were no significant differences after 30 days.

Cat scratch disease is usually self-limiting in immunocompetent children, and most do not require antibiotic therapy. Treatment is recommended for children with systemic disease with organ involvement (e.g., liver, eye), with endocarditis, or with lymphadenopathy which has not resolved after a month, or when the lymphadenopathy is associated with significant morbidity.

For treatment of cat scratch disease, azithromycin is the only antibiotic that has been compared to placebo. We recommend:

\textbf{azithromycin 10 mg/kg (max 500 mg) orally, on day 1, then 5 mg/kg (max 250 mg) orally, daily for 4 more days}

Alternative antibiotics that may be as effective include ciprofloxacin, rifampicin, co-trimoxazole (trimethoprim+sulfamethoxazole), or gentamicin.

Longer duration of treatment is necessary for endocarditis (see p. 19) and for osteomyelitis.

### 6.11 Lyme disease

Lyme disease is caused by the spirochaete bacterium, \textit{Borrelia burgdorferi}, acquired through a tick bite from the \textit{Ixodes} tick. It was first described in the USA, and is endemic in parts of the USA, Europe, the former Soviet Union, China, Japan, but not Australasia. The clinical manifestations are divided into three stages: early localized, early disseminated, and late disease.

Early localized disease manifests as erythema migrans, a rash that typically begins 7–14 days after a tick bite as a red macule or papule that expands over days or weeks to form a large, red, annular lesion, often with central clearing, with a median diameter of 15 cm. Patients with erythema migrans may also have fever, headache, malaise, myalgia, and arthralgia.\textsuperscript{84,85}

Early disseminated disease usually presents as multiple erythema migrans, which are multiple, annular lesions, smaller than the primary lesion, that appear about 4 weeks after the tick bite. They are due to bloodstream spread of the spirochaete. Early disseminated disease may present as facial nerve palsy, other cranial nerve lesions, meningitis, or conjunctivitis, all of which may occur with or without the rash.\textsuperscript{84,85} Carditis with heart block can occur in children.

Late disease presents months to years posttick bite, mainly with recurrent pauciarticular arthritis and sometimes with central nervous system (CNS) symptoms.\textsuperscript{84,85}

Culture of \textit{B. burgdorferi} is possible from the lesions, but the necessary specialized culture media are not commercially available. Diagnosis is, therefore, made serologically using enzyme immunoassay (EIA) or immunofluorescent antibodies (IFA), with confirmation of equivocal tests by Western blot.\textsuperscript{73,74} Serology is complex and should be discussed with the laboratory. The practice of sending \textit{B. burgdorferi} serology on patients with non-specific symptoms such as chronic fatigue is discouraged,\textsuperscript{73,74} because any positive results are very likely to be false positives. A systematic review of serology recommended that serology not be sent unless there was a greater than 20\% pretest probability (on clinical and epidemiologic criteria) that the patient had Lyme disease.\textsuperscript{86} CNS involvement is tested by finding CSF antibodies due to intrathecal synthesis.\textsuperscript{84,85}

A systematic review of antibiotics for early Lyme disease found 11 RCTs involving 1213 patients.\textsuperscript{87} The review suggested that phenoxymethylpenicillin, amoxicillin, amoxicillin/probenecid, tetracycline, doxycycline, and cefuroxime axetil were equally effective for treating early Lyme disease, although the available studies did not have sufficient power to detect small but
potentially clinically relevant differences in efficacy between the individual drugs. Clinical failures with erythromycin, roxithromycin, and azithromycin indicate that macrolides should not be recommended as first line agents. The studies supported the use of treatment courses of 10–21 days for early disease. Based on the systematic review and guidelines based on best available evidence, the recommended treatment for early localized disease and early disseminated disease is:

- **doxycycline child >8 years**: 2.5 mg/kg (max 100 mg) orally, 12-hourly OR
- **amoxicillin 25 mg/kg (max 1 g)** orally, 12-hourly

It is recommended to use 10–21 days for early localized disease, 21 days for multiple erythema migrans, 21–28 days for isolated facial palsy, and 28 days for arthritis.

For persistent or recurrent arthritis (defined as synovitis persisting despite 2 months’ antibiotic treatment), carditis, meningitis, or encephalitis, use:

- **ceftriaxone 100 mg/kg (max 2 g) IV, daily OR benzylpenicillin 60 mg (100,000 U)/kg (max 1.8 g or 3 million U) IV, 4-hourly**

It is recommended to use 14–28 days for persistent or recurrent arthritis or carditis, but 30–60 days for meningitis or encephalitis.

### 6.12 Prolonged fever (fever of unknown origin)

The term pyrexia of unknown origin (PUO) or fever of unknown origin (FUO) is sometimes loosely used to refer to any child with unexplained fever, however long. A traditional definition is an illness with temperature exceeding 38.3°C, evolving over a period of at least 3 weeks, with no diagnosis reached after 1 week of inpatient investigation.

The causes of FUO will vary according to whether or not the child comes from or has visited a developing country, the child’s age, referral patterns, and the sophistication of available diagnostic tests. In general, the prognosis of PUO in childhood is better than in adults.

As always, a thorough history and examination is paramount. The history should include travel, animal exposure, and potential exposure to infectious diseases, including from siblings, parents (the parental occupation may be relevant), household, and other child contacts.

In four case series from USA, Kuwait, Argentina, and Turkey, totaling 536 children with FUO, the cause was an infection in 58% of cases, collagen vascular disease in 10% (but 20% in the USA), malignancy in 6%, and other diagnoses in 11%. No diagnosis was made in 15% of children (ranging from 12% in the USA to 20% in Argentina).

#### Investigation of the child with prolonged fever

Investigation of the child with prolonged fever should be as selective as possible. Some investigations such as a full blood count, blood film, and cultures of blood and urine are mandatory. Acute phase reactants and sedimentation rate indicate inflammation and are non-specific, although very high levels may suggest endocarditis or vasculitis. A blood film should be examined for malaria parasites if the child has lived in or traveled to an endemic area (see Section 16.4, p. 257). Most children have serology performed for EBV, CMV, *Mycoplasma pneumoniae*, and any other organisms suggested by history or examination. Antinuclear antibodies and antineutrophil cytoplasmic antibodies should be measured if vasculitis is suspected. A chest X-ray and Mantoux test should usually be performed to exclude tuberculosis. Abdominal ultrasound may be helpful, especially if there is anything to indicate abdominal pathology. The yield is poor from more extensive radiologic or nuclear medicine investigations, such as CT scans, MRI, and bone scans, unless there is a clinical indication. The use of invasive investigations, such as bone marrow or liver biopsy, is dictated by clinical indications or by suggestive laboratory tests.

### 6.13 Recurrent fever

Most children with recurrent fevers without an apparent focus of infection probably have recurrent viral infections, although it is difficult to prove this. Infectious causes that should be considered and excluded if the child comes from an endemic area include malaria (see Section 16.4, p. 257), brucellosis (see Section 16.2, p. 256), and tuberculosis (see p. 198).

A number of unusual syndromes can cause periodic recurrent bouts of fever, sometimes associated with other symptoms, which have a remitting and relapsing
Table 6.2 Comparative features of some periodic fever syndromes.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PFAPA</th>
<th>FMF</th>
<th>FHF</th>
<th>Hype-IgD Syndrome</th>
<th>Systemic Onset Juvenile Arthritis</th>
<th>Cyclic Neutropenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset &lt; 5 years old</td>
<td>Usual</td>
<td>Uncommon</td>
<td>Rare</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Mean length of episodes of fever</td>
<td>4 days</td>
<td>2 days</td>
<td>Days to weeks</td>
<td>4 days</td>
<td>&gt; 30 days</td>
<td>3 days</td>
</tr>
<tr>
<td>Interval between episodes</td>
<td>2–8 weeks</td>
<td>4–8 weeks</td>
<td>Not periodic</td>
<td>Not periodic</td>
<td>Hectic quotidian</td>
<td>3–4 weeks</td>
</tr>
<tr>
<td>Aphthous ulcers</td>
<td>Usual (two-thirds of cases)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Usual</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>Yes</td>
<td>Sometimes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Cervical adenitis</td>
<td>Tender</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Sometimes</td>
<td>Yes</td>
<td>Rare</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Joint symptoms</td>
<td>Arthralgia uncommon</td>
<td>Arthralgia</td>
<td>Arthritis</td>
<td>Arthritis or arthralgia</td>
<td>Arthritis</td>
<td>No</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>Sometimes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Often</td>
<td>No</td>
</tr>
<tr>
<td>Rash</td>
<td>No</td>
<td>Erysipeloid ankle rash</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td>Not specific</td>
<td>Mediterranean</td>
<td>Irish</td>
<td>Dutch, French, or other European</td>
<td>Not specific</td>
<td>Not specific</td>
</tr>
<tr>
<td>Laboratory tests</td>
<td>None</td>
<td>Mutation in pyrin (marenostrin) gene</td>
<td>Mutation in TNF receptor genes</td>
<td>Raised serum IgD</td>
<td>Not specific</td>
<td>Intermittent neutropenia, mutation in ELA2 gene</td>
</tr>
<tr>
<td>Complications</td>
<td>None</td>
<td>Amyloidosis</td>
<td>None</td>
<td>None</td>
<td>Polyarthritis</td>
<td>Gingivitis</td>
</tr>
</tbody>
</table>

Adapted from Reference 93, with permission.

course. They can be difficult to diagnose without a high index of clinical suspicion\(^2\) (see Table 6.2).

**Familial Mediterranean fever (FMF)**

FMF is a disorder of the inflammatory response, causing intermittent widespread serositis. Mutations in the “Mediterranean fever gene” coding for a protein called pyrin or marenostrin can be demonstrated in about 85% of cases. This protein, produced mainly by neutrophils, regulates inflammation by an unknown mechanism, and gene mutations allow recurrent episodes of serositis. The inheritance of FMF is autosomal recessive, but in up to half of patients there is no family history. It characteristically affects people of Italian, Jewish, Turkish, Arabic, or Armenian ancestry, but can also occur in children with no documented Mediterranean background.\(^3\),\(^4\)

Symptoms supporting a diagnosis of FMF are:

1. episodes of fever with abdominal and/or chest and/or joint pains;
2. at least three such episodes;
3. a family history of FMF or amyloidosis.

Attacks lasting from hours to 2 or more days comprise high fevers, marked abdominal pain due to peritonitis, pleuritic chest pain, arthritis, and headaches. A characteristic rash around the ankles may also be
present. There is a risk of developing amyloidosis later. There are reports of FMF presenting in infancy, but symptoms usually start during childhood, and 80% of patients have their first attack <20 years old. The time between episodes varies. Treatment with colchicine reduces the incidence and the severity of attacks and reduces the risk of amyloidosis.94,95

**Hyperimmunoglobulin D (hyper-IgD) syndrome**

Hyper-IgD syndrome is a rare familial disorder. Attacks typically occur every 4–8 weeks, causing lymphadenopathy, abdominal pain with diarrhea, hepatosplenomegaly, arthralgia, arthritis, and a vasculitic rash. Acute phase reactants are usually markedly raised during attacks. Serum IgD is characteristically high, both during and between attacks.96,97

**Familial Hibernian fever (FHF)**

A rare but important differential diagnosis, FHF, is caused by a mutation in a tumor necrosis factor (TNF) receptor gene.98 It is dominantly inherited and affects people of non-Mediterranean background. Abdominal pain is particularly prominent, the attacks tend to occur initially at an older age, and the fever is more prolonged than in FMF. There is no response to colchicine, but steroids are effective.98

**Cyclic neutropenia**

Cyclic neutropenia is a disorder caused by a mutation in the neutrophil elastase gene. It classically results in regular episodes of high fever, often accompanied by mouth ulcers, pharyngitis, or pyogenic infections. The episodes occur every 3–4 weeks. Serial monitoring of white cell counts once weekly for 6–8 weeks shows a cyclical fall in neutrophils, with symptoms corresponding to the nadir. Heterozygous mutations in the ELA2 gene, coding for neutrophil elastase, have been described in the majority of cases of cyclic neutropenia, as well as in most cases of sporadic and autosomal dominant severe congenital neutropenia.99

**Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA syndrome)**

The diagnosis of this clinically recognized syndrome is usually made by exclusion.93,100 The etiology is not yet known. The name documents the symptoms: pharyngitis with negative throat cultures, aphthous mouth ulcers, and tender lymphadenopathy. The mean duration is 4–5 days. The child is healthy between episodes. Cyclic neutropenia needs to be excluded by measuring the white cell count during attacks. The periodicity of attacks in PFAPA syndrome is usually 4 weeks, although sometimes less, sometimes up to 6 weekly, and rarely every 3–4 months. Prednisolone 2 mg/kg daily, given for 1–2 days after onset of symptoms, is characteristically effective in aborting attacks and controlling symptoms. Cimetidine has been tried in refractory cases, with some success. Tonsillectomy is curative in up to 60% of affected children.100

**Juvenile idiopathic arthritis (JIA)**

The systemic presentation of JIA (previously called systemic Still’s disease) is often non-specific. The child has high, spiking fevers, usually once or twice a day, continuing for many days. An associated macular, orange-pink, or salmon-colored rash (really the color of smoked salmon) is highly characteristic, but is often evident only at the time of fever. There can be associated splenomegaly and lymphadenopathy. Joint symptoms are not usually prominent, and arthritis may not develop for months to years after the onset of the fever.

**References**


27 Bennish M, Been MO, Ormiste V. C-reactive protein and beta sedimentation rate as indicators of bacteremia in pediatric patients. *J Pediatr* 1984;104:729–32.


CHAPTER 7
Gastrointestinal infections

7.1 Acute gastroenteritis

Acute gastroenteritis is a common condition of childhood. It used to cause 5 million deaths a year, almost all being children younger than 5 years old in developing countries, and still causes an estimated 2 million deaths annually worldwide.¹ Gastroenteritis is potentially fatal in any country and causes about 300 deaths a year in the USA.² Rotavirus is the most important cause throughout the world, but other intestinal viruses (such as Norwalk), other noroviruses and enteroviruses, bacteria (such as Salmonella, Shigella), and Vibrio cholerae, and protozoa (such as Cryptosporidium) are also important causes.

The hallmark of acute gastroenteritis is diarrhea. Diarrhea can be defined as a change in bowel habit for the individual child, resulting in substantially more frequent and/or looser stools.¹² The diarrhea may be associated with vomiting; rotavirus gastroenteritis is characterized by 1–2 days of vomiting followed by secretory diarrhea (diarrhea which persists even if the patient takes nothing by mouth).¹

We offer two important clinical suggestions:

- **Diarrhea and/or vomiting can be non-specific presenting signs in children with systemic sepsis, e.g., meningococcal infection, septicemia, and urinary tract infection. Assess each child carefully.**

- **If a child has vomiting alone, consider the possibility of other diagnoses, e.g., intestinal obstruction (e.g., intussusception), diabetes, or meningitis, rather than assuming vomiting is due to gastroenteritis.**

Features that suggest alternate diagnoses include marked abdominal pain or tenderness, high fever (>38°C for child younger than 3 months old, >39°C for child 3 months or older), pallor, bloody diarrhea, shock, apathy, lethargy, or irritability.¹² Having urged caution, the vast majority of children with acute diarrhea, with or without vomiting, do have gastroenteritis.

Evidence-based guidelines have been published on the optimal investigation and management of acute gastroenteritis.¹⁻³

Degree of dehydration in acute gastroenteritis

**Question** | In children with gastroenteritis, can clinical examination predict accurately the degree of dehydration?

**Literature review** | We found four studies that compared clinical findings with the degree of dehydration.⁴⁻⁷

Calculation of the severity of gastroenteritis and of fluid replacement requirements requires assessment of the degree of dehydration. The degree of dehydration is proportional to the weight lost due to fluid lost. Pre-illness weight, if known, provides the most accurate measure of fluid loss. Because the pre-illness weight is not known accurately in most cases, the validity of clinical measures of dehydration has to be assessed retrospectively.

We found four studies in which clinical findings were compared with the degree of dehydration, calculated as the difference between admission weight and post-rehydration weight.⁴⁻⁷ One study was in Egypt⁵ and the other three were in North America⁶⁻⁻⁷ and Australia.⁴ In one study, a clinical score was developed to predict significant dehydration rather than relating clinical findings to weight loss.⁷

The findings of the four studies were very similar. Clinical signs of dehydration became apparent at 3–4% rather than the oft-quoted 5% dehydration. Children could be categorized as having no significant dehydration if they were <3% dehydrated, mild-to-moderate if they were about 5% dehydrated with a range of 3–8%,
Table 7.1  Assessment of degree of dehydration and recommended management.

<table>
<thead>
<tr>
<th>Minimal or No Dehydration</th>
<th>Mild to Moderate Dehydration</th>
<th>Severe Dehydration</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3% loss in body weight</td>
<td>3–8% loss in body weight</td>
<td>9% or greater loss in body weight</td>
</tr>
<tr>
<td>· No signs</td>
<td>· General appearance abnormal (“looks unwell”)</td>
<td>· Increasingly marked signs from the mild to moderate group plus:</td>
</tr>
<tr>
<td></td>
<td>· Dry oral mucosa</td>
<td>· Deep (acidotic) breathing</td>
</tr>
<tr>
<td></td>
<td>· Absent tears</td>
<td>· Altered neurological status (drowsiness, irritability)</td>
</tr>
<tr>
<td></td>
<td>· Sunken eyes</td>
<td>· Decreased peripheral perfusion</td>
</tr>
<tr>
<td></td>
<td>· Diminished skin turgor (skin recoil after pinching skin &gt; 2 s)</td>
<td>· Circulatory collapse</td>
</tr>
<tr>
<td></td>
<td>· Capillary return &gt; 2 s</td>
<td></td>
</tr>
<tr>
<td>· Manage at home generally</td>
<td>· Manage at home or in hospital with oral rehydration solution (ORS)</td>
<td>· Measure urea, electrolytes, acid–base balance</td>
</tr>
<tr>
<td></td>
<td>· If ORS not tolerated may require NG tube feeds or IV fluids</td>
<td>· Resuscitate with IV bolus if shocked</td>
</tr>
<tr>
<td></td>
<td>· Resume normal diet when tolerated</td>
<td>· Rehydrate IV over 2–6 hours with regular clinical and biochemical review</td>
</tr>
<tr>
<td>· Manage at home generally</td>
<td>· Manage at home or in hospital with oral rehydration solution (ORS)</td>
<td></td>
</tr>
<tr>
<td>· Normal fluids, continue breast-feeding, normal diet</td>
<td>· If ORS not tolerated may require NG tube feeds or IV fluids</td>
<td></td>
</tr>
<tr>
<td>· Admit if very young, diagnosis in doubt, or large losses</td>
<td>· Resume normal diet when tolerated</td>
<td></td>
</tr>
</tbody>
</table>

and severely dehydrated if they were 9% dehydrated or greater.

Doctors in industrialized countries tended to overestimate the degree of dehydration clinically. In one study, the overestimate was by a mean of 3.2%, which the authors concluded caused unnecessary hospital admissions and overtreatment with IV fluid.4

Signs associated with dehydration in two or more of the four studies are given in Table 7.1, together with advice on management.

A dehydrated child’s fluid requirements can be calculated as the volume needed to replace the deficit plus maintenance fluids plus ongoing losses.8 The volume required for daily maintenance is given in Table 7.2.

For example, if the child weighs 8 kg, the daily maintenance fluid requirements are (8 × 100) = 800 mL. If the child weighs 12 kg, the daily maintenance fluid requirements are (10 × 100) + (2 × 50) = 1100 mL. If the child weighs 23 kg, daily maintenance is (10 × 100) + (10 × 50) + (3 × 20) = 1560 mL.

Examples of calculations of replacement requirements are given in Boxes 7.1 and 7.2.

If the child is hypernatremic, there is grave risk of causing cerebral problems by giving fluid too fast.1–3 It is advised to calculate to replace the deficit over 48 hours rather than 24 hours.1–3 An RCT showed that rehydration with ORS is safer than IV fluids, with fewer complications from hypernatremia.9

A number of studies have shown that hospital doctors in an industrialized country setting tend to overestimate the degree of dehydration, leading to increased hospitalization.4,10–13 It is more dangerous to overestimate the degree of dehydration if fluids are to be replaced intravenously, because of the danger of fluid overload and serum electrolyte imbalance.

Table 7.2  Daily maintenance fluid requirements.

<table>
<thead>
<tr>
<th>Weight of Child</th>
<th>Maintenance Fluid Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>First 10 kg</td>
<td>100 mL/kg</td>
</tr>
<tr>
<td>Second 10 kg</td>
<td>50 mL/kg</td>
</tr>
<tr>
<td>Subsequent</td>
<td>20 mL/kg</td>
</tr>
</tbody>
</table>

Route of rehydration for acute gastroenteritis

Question  For children with dehydration from acute gastroenteritis, is oral rehydration as effective and safe as IV rehydration?
**Box 7.1 Example of calculation of replacement fluids for child who is 5% dehydrated.**

One-year-old child
Estimated clinically as 5% dehydrated
Weight on admission: 10 kg
Maintenance fluids: 100 mL/kg for first 10 kg

**Fluid requirements in the first 24 hours**

- Replacement: 5% of 10 kg = 500 g (which is the same as 500 mL) = 500 mL
- PLUS Maintenance fluids (100 mL/kg × 10 kg) = 1000 mL
- PLUS Ongoing losses, estimated at, say, 180 mL (guesswork) = 180 mL

**TOTAL**

Total fluid requirements = 1680 mL in first 24 hours
= 70 mL/h in first 24 hours
Recommended to be given orally using oral rehydration solution (preferably not with nasogastric tube)

---

**Box 7.2 Example of calculation of replacement fluids for child who is 10% dehydrated.**

One-year old child
Estimated as 10% dehydrated and peripherally shut down
Weight on admission: 9 kg

- Take blood for serum electrolytes, urea and creatinine, blood sugar, and full blood count
- Resuscitate using intravenous isotonic fluids: normal saline (0.9% saline) or Hartmann’s solution
- Suggest giving rapid bolus of 20 mL/kg = 180 mL
- If still poorly perfused, repeat up to total 40 mL/kg, to restore circulation
- If still shocked, consider sepsis or abdominal crisis (e.g., intussusception, perforation), continue IV infusion, admit to intensive care if possible

When child no longer shocked, and passing urine, calculate requirements for 24 hours (do not subtract resuscitation fluids)

Because of the dangers of overhydration, it is usual to calculate to replace about 5% of the deficit and review after 2–4 hours

**Fluid requirements in the next 24 hours (after circulation restored)**

- Replacement: 5% of 9 kg = 0.45 kg (which is the same as 0.45 L or 450 mL) = 450 mL
- PLUS Maintenance fluids (100mL/kg × 9kg) = 900 mL
- PLUS Ongoing losses, estimated at say 300 mL (guesswork) = 300 mL

**TOTAL**

= 1650 mL
= 69 mL/hours

As soon as possible change to oral rehydration solution for ongoing fluids, especially if child is hypernatremic
Prefer oral fluids, but may need to nasogastric fluids if child not drinking
If not tolerating enteral fluids, use IV 0.45% saline and 2.5% dextrose (higher dextrose concentration if blood sugar low), and change to oral fluids as soon as tolerated
Review the child clinically frequently, especially soon after starting and when IV fluids being given
Literature review | We found 18 RCTs, a non-Cochrane meta-analysis, and a Cochrane review comparing oral with IV rehydration.

The first meta-analysis conducted in 11 countries identified 16 trials involving 1545 children. Compared with children treated with IV rehydration, children treated with oral rehydration had significantly fewer major adverse events, including death or seizures (RR 0.36, 95% CI 0.14–0.89), and a significant reduction in length of hospital stay (mean 21 h, 95% CI 8–35 h). There was no significant difference in weight gain between the two groups (mean −26 g, 95% CI −61 to 10 g). The overall failure rate of enteral therapy was 4.0% (95% CI 3.0–5.0%). They concluded that enteral rehydration by the oral or nasogastric route is associated with significantly fewer major adverse events and a shorter hospital stay compared with IV therapy and is successful in most children.

A Cochrane review compared oral rehydration therapy (ORT) with intravenous therapy (IVT) and found 17 trials (1811 participants), all described as being of poor to moderate quality. They found more treatment failures with ORT (relative difference 4%, 95% CI 1–7). There were no significant differences in weight gain, hyponatremia or hypernatremia, duration of diarrhea, or total fluid intake at 6 and 24 hours. The ORT group stayed in hospital for 1.2 days less (95% CI −2.38 to −0.02 days). Phlebitis occurred more often in the IVT group (2%) and paralytic ileus more often in the ORT group (3%). Six deaths occurred in the IVT group and two in the ORT group.

The authors of the Cochrane review concluded that ORT and IVT were equally effective. However, although they found no clinically important differences between ORT and IVT, the ORT group did have a higher risk of paralytic ileus and the IVT group was exposed to the risks of IVT. For every 25 children treated with ORT, one would fail and require IVT.

We conclude that both oral and IV rehydration are safe and effective. In developing countries, where mothers nurse their infants and give frequent oral feeds, oral rehydration is preferred. In industrialized countries, ORT is cheaper and with fewer adverse effects. The choice may depend on the availability of parents or nursing staff to give ORT. They should be encouraged to do so, and informed that if they can give oral rehydration, the child will avoid an IV line and will get home quicker.

Rapid IV rehydration over 4 hours was advocated in the 1980s by the World Health Organization (WHO) for children in developing countries with moderate to severe dehydration, although there were no RCTs to support this recommendation. In industrialized countries, uncontrolled observational studies have looked at using rapid IVT to rehydrate children with moderate dehydration IV over 1–3 hours and send them home if they can tolerate oral fluids. A recent study concluded this practice was safe and effective, but rapid IVT has not been compared with oral rehydration, may not be safe in all hands, and is unproven in comparison to other therapies for gastroenteritis. The main advantage of rapid IV rehydration is that children recover quicker and can be sent home earlier. The main potential danger of rapid rehydration is causing fluid overload and/or electrolyte disturbances, especially if the child’s degree of dehydration is overestimated, which is common. There is also a risk of sending home some children who are in need of hospital care. There seems no reason to recommend rapid IV rehydration if oral rehydration is equally effective and has proven to be safer than IV rehydration in general.

Studies have shown that many children who could be rehydrated orally receive unnecessary IV fluids. Because doctors tend to overestimate the degree of dehydration, it is particularly important that the risks of treatment are kept to a minimum. The data suggest that oral rehydration is safer than IV fluids for hypotension and dehydration. IV cannulation may be associated with phlebitis and paralytic ileus. The main advantage of ORT is that it is less costly, less traumatic for the child, and results in a shorter hospital stay.

We recommend using oral rehydration for children with mild or moderate dehydration, although it is safe and effective to use IV fluids for children with moderate dehydration, if preferred.

Severe dehydration (9% or greater) is life-threatening and we agree with the consensus view and recommend resuscitating severely dehydrated children urgently using IV fluids.
Choice of ORS for oral rehydration in acute gastroenteritis

Since the 1980s, the WHO has recommended a standard ORS with relatively high sodium and glucose content (90 mmol/L sodium, 111 mmol/L glucose, total osmolarity 311 mmol/L). The evidence for using this composition has been questioned. A number of studies have now compared the standard WHO ORS with ORS of reduced osmolarity.

**Question**  | For children with dehydration from acute gastroenteritis, is WHO standard ORS as safe and effective as reduced-osmolarity ORS?

**Literature review**  | We found eight RCTs and a Cochrane review\(^1\) comparing standard or reduced ORS for non-cholera diarrhea. We found eight RCTs and a Cochrane review\(^2\) and one later RCT\(^3\) comparing standard or reduced-osmolarity ORS for cholera.

A Cochrane review\(^1\) found 11 studies comparing standard WHO ORS with reduced-osmolarity ORS (defined as total osmolarity 250 mmol/L or less with reduced sodium) and reported the primary outcome, which was unscheduled IV fluid infusion. In a meta-analysis of eight eligible trials, reduced-osmolarity ORS was associated with fewer unscheduled IV fluid infusions than WHO standard ORS (OR 0.59, 95% CI 0.45–0.79), with no evidence for heterogeneity between trials. Stool output was lower and vomiting was less frequent in the reduced-osmolarity ORS group. No additional risk of developing hyponatremia was found with reduced-osmolarity ORS when compared with WHO standard ORS. The meta-analysis clearly favored reduced-osmolarity ORS for non-cholera diarrhea.\(^1\)


The situation for cholera is less clear-cut, and will be considered in Section 7.4, p. 83.

**Mode of delivery of oral rehydration: oral feeds or nasogastric tube feeds**

**Question**  | For children with dehydration from acute gastroenteritis, are nasogastric tube feeds less likely to lead to treatment failure (need for IV fluids) than oral feeds?

**Literature review**  | We found six observational studies in which at least some children were rehydrated nasogastrically, but no RCTs. We found one study comparing rapid nasogastric rehydration with rapid IV rehydration.\(^2\)

The use of nasogastric tubes to give enteral feeds is increasingly common in some industrialized countries. In a retrospective study from Australia, 166 children were admitted with gastroenteritis: 20 (12%) received IV fluids, 50 (30%) received rehydration fluid orally, and 96 (58%) received rehydration fluid via a nasogastric tube.\(^2\) No patient had to be changed from enteral rehydration therapy to IVT.

A study from the USA compared rapid oral rehydration using nasogastric tube feeds with rapid IV rehydration, both giving 50 mL/kg over 3 hours.\(^2\) There were 96 children aged 3–36 months with moderate dehydration, and four treatment failures. Although the authors conclude that both treatments are safe, effective, and cost-effective, neither has been compared to simple oral feeds.

Pediatric wards in developing countries often supply a large central container of ORS so that mothers can use a ladle to get ORS and then rehydrate their children using a cup and spoon.\(^3\) Children are rehydrated without the need for interventions such as nasogastric tubes.

Nasogastric tube feeds have the advantage of getting fluid in if a child refuses to drink or is vomiting frequently. They are far less invasive, cheaper, and less traumatic then IV fluids. On the other hand, they are more invasive than oral feeds, unpleasant, and have not been shown to have any advantage over oral rehydration.

We recommend giving ORT by mouth as the first choice in the treatment of mild to moderate dehydration and that nasogastric fluids be considered if oral intake is insufficient.
Choice of IV fluids for IV rehydration in acute gastroenteritis

In many industrialized countries, it was tradition, when intravenously rehydrating children with gastroenteritis, to use low-sodium fluids (e.g., N/2 [half normal] or N/4 [quarter normal] saline) made isotonic by adding dextrose. This is because the calculated daily requirements for sodium and other electrolytes suggested that children needed only relatively low amounts of sodium for replacement compared with adults. One problem is that low-sodium fluids made isotonic by adding dextrose rapidly become hypotonic as the dextrose is rapidly metabolized. The use of low-sodium fluids was not subjected to clinical trials, and has recently been questioned, following episodes of catastrophic hyponatremia associated with IV rehydration for gastroenteritis. Hyponatremia is particularly likely to develop in children who concurrently have the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Dehydration, vomiting, and stress are potential causes of SIADH and occur commonly in gastroenteritis.23–26

Question | For children with acute gastroenteritis who need IV fluid rehydration, are low-sodium fluids safer or more effective than normal saline?

Literature review | We found a review of cases of severe hospital-acquired hyponatremia,23 a case-control study of hyponatremia,24 and one RCT comparing hypotonic with isotonic fluids.25

A 10-year review of children with severe hospital-acquired hyponatremia found over 50 reported cases of neurological morbidity and mortality, including 26 deaths, resulting from hospital-acquired hyponatremia in children who were receiving low-sodium parenteral fluids for various indications.23 These were mainly common childhood conditions requiring parenteral fluids, such as pneumonia and meningitis, dehydration, and the post-operative state. All these conditions are potential non-osmotic stimuli for antidiuretic hormone (ADH) production, which can lead to free water retention and hyponatremia. The authors concluded that the use of isotonic saline for maintenance parenteral fluids is the most important prophylactic measure that can be taken to prevent the development of hyponatremia in children who receive parenteral fluids.23 It must be remembered, however, that the authors were reporting a highly selected group of children with a predetermined outcome. There was no control group, so the study did not address whether children rehydrated with isotonic fluids might also develop hyponatremia.

A case-control study compared 40 children who developed hyponatremia in hospital over a 3-month period with children whose serum sodium remained normal.24 The patients who became hyponatremic received significantly more electrolyte-free water and had a higher positive water balance. Two of them had major neurological sequelae and one died.24

A prospective observational study looked for evidence of non-osmotic ADH activity in 52 children being rehydrated with 0.45% saline + 2.5% dextrose (“half normal” saline) for gastroenteritis.26 Serum ADH levels were raised and remained high in both hyponatremic and normonatremic children. Most children had non-osmotic stimuli of ADH secretion and the persistence of the stimulus during IV-fluid administration predisposed to dilutional hyponatremia.

We found only one RCT, in which 102 children with gastroenteritis were randomized to receive either 0.9% saline + 2.5% dextrose (NS) or 0.45% saline + 2.5% dextrose (N/2 saline) at a rate determined by their treating physician according to hospital guidelines and clinical judgment.25 Hyponatremia was common on admission (36% of patients). No child became hypernatremic after receiving IV fluids, but hyponatremia was more likely to persist or to develop in children given 0.45% saline + 2.5% dextrose than in those given normal saline. Normal saline protected against hyponatremia (no child receiving normal saline became hyponatremic) without causing hypernatremia.

For resuscitation of children with severe gastroenteritis using IV fluids, we recommend using normal saline, with or without added dextrose, to maintain the blood sugar. Hartmann’s solution would be an appropriate alternative.

Antibiotics and acute gastroenteritis

Antibiotics are not routinely recommended for acute gastroenteritis. The reasons given are that most episodes of acute gastroenteritis are caused by viruses; that most episodes are self-limiting, including those caused by bacteria; that antibiotic use for
gastroenteritis is likely to select for antibiotic resistance; and that antibiotics might increase gastrointestinal motility and cause bacterial overgrowth and thus worsen diarrhea.

**Question**  
For children with acute gastroenteritis, do antibiotics compared with no antibiotics or placebo speed recovery?

**Literature review**  
We found one placebo-controlled RCT of erythromycin\(^7\) and two adult studies of ciprofloxacin for acute gastroenteritis.\(^8,9\)

A small RCT of erythromycin for gastroenteritis in infancy showed no significant clinical benefit.\(^7\) Two RCTs of ciprofloxacin in adults with acute diarrhea did describe modest clinical benefits, but because of the risk of rapid development of quinolone resistance\(^10\) and the risk of adverse effects from quinolones in children, the use of antibiotics in this setting is not justified.\(^8,9\)

We found no evidence to support the routine use of antibiotics for gastroenteritis in children. Traveler’s diarrhea (Section 7.10, p. 86) and gastroenteritis due to specific organisms will be considered below.

**We do not recommend antibiotics routinely for acute childhood gastroenteritis.**

**Antiemetics in acute gastroenteritis**  
A Cochrane review\(^11\) of antiemetics for children with gastroenteritis found two RCTs, with a total of 181 children. Ondansetron and metoclopramide reduced the number of episodes of vomiting due to gastroenteritis in children compared to placebo, but increased the incidence of diarrhea.\(^12,13\) We do not recommend antiemetics in childhood gastroenteritis.

**Diet in acute gastroenteritis**  
Recommendations for maintenance dietary therapy in gastroenteritis depend on the age and diet history of the patient.

**Breast-feeding and gastroenteritis**  
There is widespread consensus that breast-fed babies with dehydration from gastroenteritis should be rehydrated orally (with ORS) or intravenously, but should continue breast-feeding.\(^1\) The reasons are to maintain adequate nutrition and to maintain breast-feeding. There are no RCTs, but this recommendation is an empirical one, which is unlikely to be studied in an RCT.

**We recommend that breast-fed infants with acute gastroenteritis should continue breast-feeding on demand.**

**Lactose-free formula feeds and acute gastroenteritis**  
**Question**  
For babies with acute gastroenteritis, do lactose-free or lactose-reduced feeds, compared with breast milk or lactose-containing formulas, speed recovery?

**Literature review**  
We found 29 RCTs and a non-Cochrane meta-analysis.\(^14\)

Breast milk contains as much lactose as formula feeds. Despite this, many people advocate low lactose or lactose-free formulas, supposedly because of the risk of lactose intolerance secondary to gastroenteritis. A meta-analysis of 29 RCTs (2215 patients) found no advantage of lactose-free formulas over lactose-containing formulas for the majority of infants, although infants with malnutrition or severe dehydration recovered more quickly when given lactose-free formula.\(^14\)

Lactose intolerance often occurs post-gastroenteritis, due to damage to the mucosa resulting in impaired production of the lactase enzyme used to metabolize lactose, but is usually transient and does not require treatment. Patients with persistent lactose intolerance will have exacerbation of diarrhea when a lactose-containing formula is introduced. The presence of low pH (<6.0) or reducing sub-stances (>0.5%) in the stool is not diagnostic of lactose intolerance in the absence of clinical symptoms.\(^1\)

**We recommend that lactose-free or lactose-reduced formulas are not routinely used for acute gastroenteritis and should be given only when there is evidence of lactose intolerance.**

**Regrading and acute gastroenteritis**  
Although medical practice has often favored restarting feeds with diluted (e.g., half- or quarter-strength) formula (“regrading feeds”), controlled clinical trials have shown that this practice is not only unnecessary but prolongs symptoms\(^15\) and delays nutritional recovery.\(^16\)

**We do not recommend using diluted feeds for children recovering from gastroenteritis.**
Soy fiber and acute gastroenteritis
Formulas containing soy fiber have been marketed, particularly to physicians and consumers, in the USA. Added soy fiber has been reported to reduce liquid stools without changing the overall stool output. This cosmetic effect might reduce diaper rash and encourage early resumption of normal diet, but the benefits are probably insufficient to merit its use as a standard of care.1

Solids and gastroenteritis
Children receiving semisolid or solid foods should continue to receive their usual diet during episodes of diarrhea. Routinely withholding food for a day or more, which is sometimes advocated, is inappropriate. Early feeding reduces changes in intestinal permeability caused by infection,38 reduces the duration of illness, and improves nutrition.39,40 Severe malnutrition can occur after gastroenteritis if prolonged gut rest or clear fluids are prescribed.41 This is a particular problem in developing communities where children often experience many episodes of gastroenteritis and catch-up growth is not achieved between episodes.

Zinc in diarrheal diseases
Severe zinc deficiency is associated with diarrhea (acrodermatitis enteropathica), which prompted studies on the role of zinc supplementation in preventing and treating acute and chronic diarrhea. In developing countries, prophylactic dietary oral zinc supplementation reduces the incidence and severity of acute diarrheal disease in childhood.42,43 Furthermore, oral zinc supplements reduce the duration of chronic diarrhea in developing countries.44,45 A systematic review identified five RCTs of oral zinc supplementation for chronic diarrhea in developing countries.45 Zinc-supplemented children had a 24% lower probability of continuing diarrhea (95% CI 9–37%) and a 42% lower rate of treatment failure or death (95% CI 10–63%).45

For acute diarrhea, a meta-analysis found five RCTs of the use of oral zinc supplements started at the time children presented with acute diarrhea in developing countries. Zinc-supplemented children had a 15% lower probability of continuing diarrhea on a given day (95% CI 5–24%).45 These benefits were independent of concomitant vitamin A supplementation.43–50 Neither zinc nor vitamin A supplementation, however, influenced the duration of acute diarrhea or the rate of readmission with diarrhea in Australian Aboriginal children.51

The WHO recommends that oral zinc is given to children in developing countries at the onset of diarrhea.

Vitamin A
The effect of routine dietary vitamin A supplementation on the incidence of diarrheal disease in infants in developing countries is controversial. Large doses of vitamin A have been associated with an increased risk of diarrhea,52 while other studies showed reduced incidence of diarrhea.53 A meta-analysis of nine RCTs found that supplemental vitamin A had no consistent benefit on the incidence of diarrhea (RR 1.00, 95% CI 0.94–1.07) and was associated with a slight increase in the incidence of respiratory infections.54 Vitamin A supplements do not influence the outcome of acute diarrheal illness.45–50

We do not recommend vitamin A in acute gastroenteritis.

Probiotics in acute gastroenteritis

Question | For children with acute gastroenteritis, do probiotics compared to no probiotics or placebo shorten the duration of diarrhea?

Literature review | We found a Cochrane review of probiotics in adults and children,55 a non-Cochrane systematic review of probiotics in children,56 and a meta-analysis of lactobacilli in children.57

Probiotics are live microorganisms in fermented foods or components of microbial cells that have a beneficial effect on the health and well-being of the host.55 Examples studied in trials include various species of lactobacilli or bifidobacteria and the non-pathogenic yeast Saccharomyces boulardii. No serious adverse effects of probiotics have been reported in well people, but infections have been reported in people with impaired immune systems.55

One systematic review restricted to placebo-controlled RCTs of probiotics in treating acute diarrhea in infants and children found 8 trials (731 children).56 Probiotics reduced the risk of diarrhea lasting 3 or more
days by 60% and reduced the duration of diarrhea by 18 hours. A meta-analysis restricted to RCTs of lactobacilli in children found 7 studies (675 children). Lac-
tobacilli reduced the duration of diarrhea by 0.7 days. Heterogeneity of results between studies prevented the
analysis of the effects of individual strains of lacto-
bacilli. A Cochrane review that included adult and child
RCTs found 23 studies (1917 patients). Probiotics re-
duced the risk of diarrhea at 3 days by 34% and the
mean duration of diarrhea by 30.5 hours. There was
some heterogeneity.

The CDC advise caution, pointing out that because
dietary supplements like probiotics are usually not
regulated by the federal government, the potential ex-
ists for great variability among them, providing a chal-
lenge to the prescribing physician to make an informed
recommendation regarding their use. We conclude
that further research is needed to determine the op-
timal type, dosage, and regimen.

**We do not recommend routine use of probiotics
for prevention or treatment of acute
gastroenteritis, but we feel it is likely that their
benefit outweighs their harm.**

**Nitazoxanide in acute gastroenteritis**

Nitazoxanide is a thiazolide anti-infective active against
protozoan parasites ( *Giardia, Entamoeba histolytica,
Cryptosporidium, Blastocystis*) and against *Clostridium
difficile*. It was studied in rotavirus gastroenteritis in
Egypt. In a small RCT, 38 children, aged 5 months to
7 years (median age 11 months), hospitalized for gas-
troenteritis, with rotavirus as the sole identified cause,
were randomly assigned to either 7.5 mg/kg nitazox-
anide as an oral suspension or placebo twice a day
for 3 days. Nitazoxanide was associated with a signif-
icant reduction in time to resolution of illness to 31
hours compared with 75 hours for the placebo group.
No significant adverse events were reported. The au-
thors also performed in vitro studies which showed
that tizoxanide, a metabolite of nitazoxanide, was po-
tent at inhibiting rotavirus replication. Nitazoxanide
may be acting as an antiviral agent or may be treat-
ing occult parasitic infection. The study is small and
the main author is an employee and stockholder of the
company that owns the intellectual property rights for
nitazoxanide, and so the results should be interpreted
with caution.

**Emergency department guidelines on
management of acute gastroenteritis**

Developing evidence-based guidelines is common.
Evaluating the effect of their implementation is far less
common. A British group developed guidelines based
on best evidence and consensus view and then sought
the opinion of the guidelines from a panel of 39 selected
medical and nursing staff using a postal Delphi con-
sensus process. When the guidelines were introduced
in a pediatric emergency department, oral rehydration
was used more appropriately and there was a reduction
from 9 to 1% in the proportion of children receiving
unnecessary IV infusions. Management time in the
emergency department was reduced from 55 to 40 min-
utes and documentation improved. The proportion of
children investigated with unnecessary blood tests fell
from 11 to 4%. Surprisingly, however, the admission
rate for diarrhea increased from 27 to 34%. This study
shows the importance of evaluating the effect of guide-
lines, however well-meaning, after they have been in-
duced to make sure that they are effective and do
not have unexpected effects.

**7.2 Antibiotic-associated
diarrhea**

In most cases of antibiotic-associated diarrhea no
pathogen is identified, although toxin produced by *C.
difficile* is responsible for a minority. Stopping antibi-
otics usually relieves the problem. Dietary manipu-
lation may help. In a masked, randomized parallel study,
older infants and toddlers with diarrhea which devel-
oped when receiving antibiotics were fed commercial
soy formulas with or without added soy fiber for 10
days. The mean duration of diarrhea was significa-
tly reduced from 51.6 hours for those fed the regular for-
ma to 25.1 hours for children fed the formula with
added fiber.

A Cochrane review of nine studies of *C. difficile-
associated diarrhea in adults suggested that mild cases
do not need specific treatment, while metronidazole
was as effective as vancomycin and other antibiotics in
treating severe cases. If it is not possible to stop an-
tibiotics, it is recommended to change to a regimen less
likely to cause diarrhea. Amoxicillin, broad-spectrum
cephalosporins, quinolones, and some other broad-
spectrum antibiotics (e.g., ticarcillin + clavulanate) are
the antibiotics most commonly associated with diarrhea.

When *C. difficile* is proven or suspected in symptomatic patients, we recommend:

**metronidazole 10 mg/kg (max 400 mg) orally, 8-hourly for 7–10 days**

*C. difficile* or its toxins can occasionally be demonstrated in asymptomatic infants, especially newborns, and some older children. Treatment for asymptomatic carriage is not indicated.

Metronidazole is preferred to vancomycin because of the dangers of selecting for vancomycin-resistant organisms, particularly vancomycin-resistant enterococci, by the use of non-absorbable vancomycin. If, however, the diarrhea does not respond, relapses, or is particularly severe, we recommend:

**oral vancomycin 10 mg/kg (max 125 mg) orally, 6-hourly for 7–10 days**

Quinolones are effective, but resistance develops rapidly. In one study, *Campylobacter* with high-level resistance to norfloxacin appeared in three of eight patients within 4–90 days of starting norfloxacin.  

Azithromycin was at least as effective as ciprofloxacin for adult travelers with *Campylobacter* infection, but is more expensive than erythromycin, and has not been compared to placebo.

Antibiotic therapy is indicated only when there is high fever or severe illness, suggesting septicemia, usually in infants. If antibiotics are indicated, we recommend:

**erythromycin 10 mg/kg (max 500 mg) orally, 6-hourly OR azithromycin 10 mg/kg (max 500 mg) orally, daily**

For proven *Campylobacter* bacteremia, base antibiotics on susceptibility results. For suspected bacteremic disease, we recommend:

**gentamicin <10 years: 7.5 mg/kg IV daily, 10 years or older: 6 mg/kg IV daily OR ciprofloxacin 10 mg/kg (max 400 mg) IV 12-hourly**

### 7.3 *Campylobacter enteritis*

**Question** | For children with gastroenteritis due to *Campylobacter*, do antibiotics compared with no antibiotics or placebo speed recovery?

**Literature review** | We found four placebo-controlled trials of erythromycin for *Campylobacter*,  

Three studies found that erythromycin shortened excretion of *Campylobacter*, but had no clinical effect on duration of diarrhea. One study found that erythromycin hastened the cessation of diarrhea. Campylobacter enteritis is usually self-limited. Antibiotics have relatively little clinical benefit and because of the risk of resistance are not routinely indicated.

**7.4 Cholera**

Rehydration is the basis of cholera treatment and can usually be achieved orally despite massive ongoing losses. A Cochrane review of seven trials (718 participants) found that hyponatremia, defined as serum sodium <130 mmol/L, was more common with reduced-osmolarity ORS than with standard ORS (RR 1.67, CI 1.09–2.57). This did not reach significance for severe hyponatremia, defined as serum Na <125 mmol/L (RR 1.58, CI 0.62–4.04). No trials reported symptomatic hyponatremia or death. No statistically significant difference was found in the need for unscheduled IV infusion. Analyses separating children and adults showed no obvious trends. Two trials (102 participants) examined rice-based ORS. In the reduced-osmolarity group, duration of diarrhea was shorter (weighted mean difference −16.85 h, CI −21.22 to −12.48). A later trial of 176 patients aged 12–60 years with cholera found no difference in serum sodium or risk of hyponatremia, but patients treated with reduced-osmolarity ORS had a significantly lower
volume of vomiting and significantly higher urine output than those treated with standard WHO ORS.19

A meta-analysis of 13 trials showed that rice-based ORSs significantly reduce the rate of stool output during the first 24 hours by 36% (95% CI 28–44%) in adults with cholera and by 32% (19–45%) in children with cholera.68 The benefit of rice-based ORS in cholera was confirmed in a Cochrane review of 15 trials69 and one subsequent RCT.70 Rice-based ORS is far less effective for non-cholera diarrhea, for which it is not recommended.68,69

We recommend using standard WHO ORS or rice-based ORS for children with cholera diarrhea.

Antibiotic therapy reduces the volume and duration of cholera diarrhea.71,72 Single-dose ciprofloxacin achieves similar or better clinical outcomes than 12-dose erythromycin in children with cholera, but is less effective in eradicating V. cholerae from stool.71 Single-dose azithromycin is as effective as erythromycin and causes less vomiting. We recommend:

- azithromycin 20 mg/kg orally as a single dose OR
- doxycycline child >8 years: 2.5 mg/kg (max 100 mg) orally, 12-hourly for 3 days OR
- ciprofloxacin 25 mg/kg (max 1 g) orally as a single dose OR
- erythromycin 12.5 mg/kg (max 500 mg) orally, 6-hourly for 3 days

Antibiotic-resistant strains are now common in some regions, where antibiotics different to those recommended above may be needed.

7.5 Enterohemorrhagic E. coli (EHEC) enteritis

Most E. coli infections cause self-limiting watery diarrhea which does not require specific therapy. Infection with some EHEC strains, e.g., O157:H7 and O111:H8, can lead to the development of hemolytic uremic syndrome or thrombotic thrombocytopenic purpura.

The use of antibiotics is controversial. A systematic review of E. coli O157:H7 infections reported that most isolates are susceptible in vitro to various antibiotics, but that certain antibiotics, especially at sublethal concentrations, increase the release of Shiga-like toxins, which have been associated with the development of hemolytic uremic syndrome/thrombotic thrombocytopenic purpura in humans.73 Most of the clinical studies involve small numbers of patients. No studies have shown that antibiotics are effective in reducing the duration of E. coli O157:H7 infection or the duration of diarrhea or bloody diarrhea. A few studies have supported that some antibiotics, especially quinolones and fosfomycin, may prevent the development of hemolytic uremic syndrome or thrombotic thrombocytopenic purpura. On the other hand, some clinical studies associate antibiotics with a higher risk for hemolytic uremic syndrome and/or longer duration of diarrhea, and even with an increased mortality.74

We recommend that antibiotics should not be prescribed routinely for children with EHEC infection or hemolytic uremic syndrome.

7.6 Enteropathogenic Escherichia coli (EPEC) enteritis

In a setting where there was a high prevalence of an EPEC (serotype O111:B4), an RCT of infant diarrhea showed a clinical cure on the third day in 79% given mecillinam, 73% trimethoprim-sulfamethoxazole, but only 7% given placebo.74 This is an uncommon situation. Most EPEC infections occur in developing countries and the organism is never cultured. The main significance is for traveler’s diarrhea (see Section 7.10, p. 86).

7.7 Non-typhoid Salmonella enteritis

Question | For children with gastroenteritis due to non-typhoid Salmonella (NTS), do antibiotics compared with no antibiotics or placebo speed recovery?

Literature review | We found 12 RCTs and a Cochrane review29 comparing the use of antibiotics with placebo for NTS infection.

In industrialized countries, most NTS infections are food-borne, causing acute gastroenteritis alone; extraintestinal complications, such as septicemia, meningitis, and osteomyelitis, are rare.75 Outbreaks are associated especially with infected food from poultry (meat or eggs), cattle and pigs, and from infections contracted abroad. In contrast, in developing countries,
particularly tropical Africa, NTS are an important cause of invasive extraintestinal disease. Rates of *Salmonella* infection appear to be falling in industrialized countries, but this is counterbalanced by an alarming rise in multiresistant strains, which are associated with increased morbidity and mortality. A Cochrane review of trials of antibiotics for NTS infections found 12 RCTs. There were no significant differences in length of illness, diarrhea, or fever between any antibiotic regimen and placebo. Antibiotic regimens resulted in more negative cultures during the first week of treatment but clinical relapses were more frequent in those receiving antibiotics, and antibiotics prolonged salmonella detection in stools after 3 weeks. Adverse drug reactions were more common in the antibiotic groups. These studies included the newer antibiotics such as quinolones.

We recommend that children with uncomplicated NTS infection are not given antibiotics.

Antibiotics are not indicated for asymptomatic short-term carriers. However, antibiotic therapy is indicated for patients who are proven or suspected to be septicemic. Septicemia is more likely in malnourished infants, infants <3 months old, and immunosuppressed children. If a child with any of these conditions presents with bloody diarrhea and fever and/or has *Salmonella* isolated from feces, antibiotics are recommended, although their value is assumed rather than proven. Antibiotics are also recommended for *Salmonella* infection occurring in association with chronic gastrointestinal disease, malignant neoplasms, hemoglobinopathies, or severe colitis.

The choice of antibiotic to start and to continue treatment should be based on culture results. Amoxicillin is preferred if the organism is susceptible. For empiric therapy we recommend:

- ciprofloxacin 10 mg/kg (max 500 mg) orally, 12-hourly OR
- azithromycin 20 mg/kg (max 1 g) orally on the first day, then 10 mg/kg (max 500 mg) daily

The appropriate duration of therapy has not been defined, but 5–7 days is usually effective.

If oral therapy cannot be tolerated until oral antibiotics (as above) can be tolerated, we recommend:

- ciprofloxacin 10 mg/kg (max 400 mg) IV, 12-hourly OR
- ceftriaxone 50 mg/kg (max 2 g) IV daily

### 7.8 Typhoid and paratyphoid fevers (enteric fevers)

Typhoid and paratyphoid fevers, due to *Salmonella typhi* and *S. paratyphi*, respectively, are endemic in many developing countries. Almost all infections in industrialized countries are acquired by travelers, although very occasionally cases occur with no history of travel. In these cases, enquiries should be made about contact with travelers, food exposure, and about contact with family members who work in laboratories (laboratory-acquired cases occur and can be transmitted).

Typhoid is a septicemic illness rather than a diarrheal illness, but will be covered in this section. The clinical features in children have been described in a number of studies, each of over 100 children. Typhoid affects children from infancy to adolescence, with a median age of 6–8 years. Fewer than 2% of cases are in infants, and they have the highest mortality. The most common clinical features are fever, hepatomegaly, abdominal pain, diarrhea, vomiting, cough, malaise, and headache. Hepatomegaly is more common than splenomegaly. Rose spots are rare and children do not have relative bradycardia. Other manifestations of typhoid include febrile convulsions, jaundice, ileus, perforation, and impaired consciousness. Hematologic abnormalities include neutropenia, leucopenia, and thrombocytopenia. The organism can be grown from blood, feces, or urine. Serology can be useful, but more often to make a retrospective diagnosis than in acute diagnosis.

Multidrug resistance is an increasing problem. A Cochrane review of fluoroquinolones for typhoid fever found 33 trials, but study methodology was often poor, and although typhoid mainly affects children, only 3 trials exclusively studied children. The Cochrane review found that quinolones were at least as effective as chloramphenicol, co-trimoxazole,
ceftiraxone, cefixime, and azithromycin in adults. In trials of hospitalized children, fluoroquinolones were not statistically significantly different from ceftriaxone or cefixime. Treatment with norfloxacin resulted in clinical failure more often than treatment with other fluoroquinolones. Trials comparing different durations of fluoroquinolone treatment showed no statistically significant differences,86,87 and two pediatric studies showed 2 days of ofloxacin was safe and highly effective in uncomplicated typhoid in children.88,89

Short-course (5 days) oral azithromycin was as effective as ceftriaxone in acute cure,85 and clinical relapses occurred only with ceftriaxone but not azithromycin.90,91 In Pakistan, the relapse rate was higher (14%) with 7 days than 14 days of ceftriaxone.92 Although in vitro studies suggest that almost all isolates are sensitive to quinolones,89–92 there are increasing reports of clinical failures when using quinolones to treat infections acquired in the Indian sub-continent and in Vietnam. For the treatment of typhoid and paratyphoid fevers acquired in other areas, we recommend:

- **ciprofloxacin 15 mg/kg (max 500 mg) orally, 12-hourly for 7–10 days** OR
  - in uncomplicated disease, EITHER
  - **ofloxacin 10 mg/kg (max 400 mg) orally, daily for 2 days** OR
  - **azithromycin 20 mg/kg (max 1 g) orally, daily for 5 days**

If oral therapy cannot be tolerated, initial therapy, until oral can be tolerated, should be with:

- **ciprofloxacin 10 mg/kg (max 400 mg) IV, 12-hourly** OR
- **azithromycin 20 mg/kg (max 1 g) IV, daily**

Fever often persists for several days with both NTS and typhoid infections, even if using appropriate antityphoid antibiotics, and is less concerning if the child’s clinical state is much improved.89–92 Ibuprofen may be more effective than paracetamol at reducing fever in typhoid fever.93

If reduced susceptibility to ciprofloxacin is suspected because of country of acquisition, or is reported by the laboratory (nalidixic acid resistant), or the clinical response is delayed (e.g., child remains unwell or fever >7 days), we recommend:

- **ceftiraxone 50 mg/kg (max 2 g) IV, daily OR, in uncomplicated disease**
- **azithromycin 20 mg/kg (max 1 g) IV or orally, daily for 5 days**

If the organism is sensitive and the child is improving, we recommend oral amoxicillin or oral azithromycin.

### 7.9 Shigellosis

Antibiotic therapy is recommended for children with shigella dysentery, even if mild, for public health reasons because a very low inoculum causes infection and because antibiotics eliminate the organism. It is stated that antibiotics relieve symptoms, but although we found 34 studies of antibiotics in shigellosis, 16 of them in children, all the studies compared different antibiotics or different doses or duration or different routes of administration. We found no studies that compared antibiotic with placebo or no antibiotics.

Effective antibiotics, if the organism is sensitive, include quinolones,94,95 ceftriaxone,94 azithromycin,96,97 cefixime,95 and cotrimoxazole.98 A study in Zimbabwe showed that 3 days of ciprofloxacin was as effective as 5 days in Shigella dysenteriae type 1 infection, and all children had bacteriologic cure without relapse.95

The pattern of antibiotic susceptibility of *Shigella* strains varies from country to country, and multidrug-resistant strains are encountered in many regions. Antibiotic therapy should be modified according to the results of culture and susceptibility tests:

- **ciprofloxacin 15 mg/kg (max 600 mg) orally, 12-hourly for 3 days** OR
- **azithromycin 20 mg/kg (max 1 g) one dose, then 10 mg/kg (max 500 mg) orally, daily for 4 days** OR
- **trimethoprim + sulfamethoxazole 4 + 20 mg/kg (max 160 + 800 mg) orally, 12-hourly for 5 days**

### 7.10 Traveler’s diarrhea

Traveler’s diarrhea is a common problem, with an attack rate of 20–50% of travelers to high-risk countries. It has been estimated that at least 11 million people annually develop traveler’s diarrhea.99–101
A working definition is the passage of three or more unformed stools over 24 hours, with symptoms starting during or shortly after a period of foreign travel. The diarrhea is often accompanied by nausea, vomiting, abdominal pain, fever, tenesmus, and blood or mucus in the stools.

Organisms can be isolated from about 50% of episodes of traveler’s diarrhea and about 85% of the organisms are bacteria, although the relative importance of different pathogens varies according to the region visited and the season. Worldwide, enterotoxigenic E. coli (ETEC) are the most common bacterial pathogens isolated. Two-thirds of ETEC produce a heat-labile toxin similar to cholera toxin which induces secretory diarrhea. Campylobacter jejuni is an ubiquitous pathogen that causes up to 30% of all cases of traveler’s diarrhea, particularly in Asia. Salmonellae and shigellae each account for up to 15% of cases, and enteroinvasive E. coli are increasingly recognized as possible causes of traveler’s diarrhea.

Prevention of traveler’s diarrhea

Prevention can be difficult. “Boil it, cook it, peel it, or forget it” is time-honored advice, but studies do not show that dietary advice is followed or effective.

Contaminated water is probably the major source of traveler’s diarrhea. Standard advice to travelers to low-income countries is to avoid drinking the local water. Tap water and ice cubes should be thought of as contaminated. The latter may contain organisms such as Shigella, which have a very low infective dose. Boiling is the most effective way of ensuring that water is safe to drink. Buying bottled water is not totally safe, because empty bottles may be filled with tap water and recycled as if new. Chlorine tablets can be used to purify tap water, which sacrifices palatability for safety: the purified water can be drunk and used to clean teeth. Swimming pool water is also a potential risk, while rivers, standing freshwater, and seawater may be contaminated by sewage. Swimmers are advised to avoid sub-merison or swallowing water.

Because of the widely varying causes of traveler’s diarrhea, the chances of developing an effective vaccine for prophylaxis are limited, although a combination vaccine against ETEC, Campylobacter, and Shigella might be useful in the future. The only combination vaccine currently available is an oral, killed, recombinant B sub-unit, whole-cell vaccine against cholera and ETEC. Basic immunization for adults and children comprises two doses of vaccine given at an interval of at least 1 week, and satisfactory protection against cholera and ETEC diarrhea can be expected about 1 week after the second dose. There are no efficacy data in children. A study of 615 adult tourists who went to Morocco from Finland showed 52% protection against traveler’s diarrhea associated with ETEC strains and 71% protective efficacy against a combination of ETEC and any other pathogen.

Another efficacy study of 502 US students traveling to Mexico showed 50% protective efficacy against all ETEC strains, regardless of toxin type. However, ETEC cause only 20–40% of episodes of traveler’s diarrhea, so the vaccine will prevent <30% of all cases of traveler’s diarrhea. The vaccine is licensed as Dukoral for protection against traveler’s diarrhea in only a few countries including Sweden and Canada.

Prophylactic antibiotics are not recommended for healthy travelers and not for children. Antibiotic prophylaxis might be considered for an immunocompromised child traveling for a relatively short time, in which case a fluoroquinolone (ciprofloxacin or norfloxacin) would be the antibiotic of choice.

Treatment of traveler’s diarrhea

Question For children with traveler’s diarrhea, does empiric antibiotic therapy compared with no antibiotics or placebo shorten the illness?

Literature review We found 12 RCTs and a Cochrane review.

A Cochrane review of empiric therapy for traveler’s diarrhea found 20 trials (12 placebo-controlled) in which travelers >5 years old with acute non-bloody diarrhea due to unknown organism at allocation were randomly allocated to treatment with antibiotics or placebo. All of the trials reported a significant reduction in duration of diarrhea in participants treated with antibiotics compared with placebo. The trials generally did not report duration of post-treatment diarrhea. Persons taking antibiotics experienced more side effects than those taking placebo. The most effective antibiotics for empiric therapy from trials are quinolones, azithromycin, and rifaximin.
As with other types of diarrhea, all patients should take fluids and electrolytes. Rehydration with ORS is particularly important for young children.

Antimotility drugs, such as loperamide, should be avoided in children, because of the danger of causing paralytic ileus. Mild cases do not usually need antibiotics. For moderate to severe disease, we recommend:

- azithromycin 20 mg/kg (max 1 g) orally, as a single dose OR
- ciprofloxacin 20 mg/kg (max 750 mg) orally, as a single dose OR
- norfloxacin 20 mg/kg (max 800 mg) orally, as a single dose OR
- trimethoprim + sulfamethoxazole 4 + 20 mg/kg (max 160 + 800 mg) orally, 12-hourly for 3 days OR
- rifaximin 10 mg/kg orally, 12-hourly for 3 days

If after the above, diarrhea continues or if fever or bloody stools are present, we recommend up to 3 days therapy with:

- azithromycin 10 mg/kg (max 500 mg) orally, once daily OR
- norfloxacin 10 mg/kg (max 400 mg) orally, 12-hourly OR
- ciprofloxacin 10 mg/kg (max 500 mg) orally, 12-hourly

The management of persistent diarrhea in a returned traveler depends on accurate diagnosis of the responsible pathogen(s) or identification of a non-infective cause. Investigations should include stool microscopy and culture. Multiple stool samples may be required to diagnose some parasitic infections. Serology may be helpful in some cases, e.g., amebiasis, schistosomiasis, strongyloidiasis. If no clear diagnosis is identified, empiric therapy for giardiasis should be considered, given the difficulties in diagnosis. If symptoms persist, specialist advice should be sought.

### 7.11 Protozoal infections

#### Amebiasis (*Entamoeba histolytica*)

*E. histolytica* infection can cause non-invasive intestinal infection, which can be asymptomatic or cause amebic dysentery or colitis, ameboma, and/or liver abscess. Passage of *Entamoeba* cysts or trophozoites in the absence of acute dysenteric illness does not warrant antimicrobial therapy, although some authorities recommend a luminal agent (paromomycin, diloxanide furoate, or iodoquinol; see p. 89) for chronic cyst excretors.

**Amebic dysentery**

Patients with amebic colitis characteristically present with dysenteric symptoms of bloody diarrhea, abdominal pain, and tenderness. Children can have rectal bleeding without diarrhea. The onset can be gradual, with several weeks of symptoms: often multiple, small volume, mucoid stools, but sometimes profuse, watery diarrhea. Occasionally, individuals develop fulminant amebic colitis, with profuse bloody diarrhea, fever, pronounced leukocytosis, widespread abdominal pain often with peritoneal signs, and extensive involvement of the colon. Paralytic ileus and concurrent amebic liver abscess may occur. Toxic megacolon complicates amebic colitis in about 0.5% of patients. The main danger is intestinal perforation, which occurs in >75% of individuals with fulminant amebic colitis, with a mortality over 40%. Amebomas are localized inflammatory, annular masses of the cecum or ascending colon which can cause obstruction and be confused with carcinomas. Patients on corticosteroids are at particular risk if they develop amebiasis.

The diagnosis of amebic colitis rests on the demonstration of *E. histolytica* in the stool or colonic mucosa of patients with diarrhea. Stool microscopy cannot distinguish between *E. histolytica* and *E. dispar*, but is still useful in the correct clinical setting such as a child with bloody diarrhea. Commercially available ELISA assays which not only identify *E. histolytica* antigens in stool but distinguish *E. histolytica* from *E. dispar* are more sensitive and less user-dependent than microscopy. However, they are not generally used in endemic areas and their reported sensitivity and specificity still need to be confirmed with independent studies. Stool polymerase chain reaction (PCR) may be used in the future. Some patients with acute colitis, especially when amebiasis is suspected on clinical grounds but *E. histolytica* is not initially detected in stools, will benefit from colonoscopy or flexible sigmoidoscopy with examination of scrapings and biopsy samples for amebic trophozoites.

Serum antibodies against amebae are detected by indirect hemagglutination in >70% of patients with
symptomatic *E. histolytica* infection and are particularly sensitive (>94%) in amebic liver abscess. Serology can be useful when there is diagnostic uncertainty. In some gastroenterology departments, *E. histolytica* serology is performed routinely on all patients with bloody diarrhea, and positive ameba serology has saved more than one child with amebiasis but with a wrong clinical diagnosis of inflammatory bowel disease from a colectomy.

For acute amebic dysentery, the nitroimidazoles (metronidazole, tinidazole, ornidazole) are >90% effective. Tinidazole is at least as effective as metronidazole, more effective in some studies, and better tolerated, but is not available in the USA. We recommend:

- **metronidazole 15 mg/kg (max 600 mg) orally, 8-hourly for 7–10 days OR**
- **tinidazole 50 mg/kg (max 2 g) orally, daily for 3 days**

To eradicate cysts and prevent relapse after acute treatment, if available, follow with:

- **paromomycin 10 mg/kg (max 500 mg) orally, 8-hourly for 7 days OR**
- **diloxanide furoate 7 mg/kg (max 500 mg) orally, 8-hourly for 10 days OR**
- **iodonoquil 10 mg/kg (max 650 mg) orally, 8-hourly for 20 days**

**Amebic liver abscess**

Amebic liver abscess may be diagnosed clinically and radiologically and confirmed serologically. In this case, therapeutic aspiration may be required as an adjunct to specific antiparasitic therapy. Drainage of the abscess should be considered in patients who have no clinical response to drug therapy within 5–7 days or those with a high risk of abscess rupture, as defined by a cavity with a diameter of more than 5 cm or by the presence of lesions in the left lobe. Drainage may also identify the rare child with bacterial coinfection of an amebic liver abscess. Imaging-guided percutaneous treatment (needle aspiration or catheter drainage) has replaced surgical intervention as the procedure of choice for reducing the size of an amebic liver abscess.

For amebic liver abscess, we recommend:

- **metronidazole 15 mg/kg (max 600 mg) orally, 8-hourly for 14 days OR**
- **tinidazole 50 mg/kg (max 2 g) orally, daily for 5 days**

**Blastocystis hominis**

There is controversy about the pathogenicity of *Blastocystis hominis*, a parasite that can be recovered from 1 to 20% of stool specimens tested for ova, cysts, and parasites. It is generally considered to be a commensal and it is usually recommended to ignore its presence in stools. We found one placebo-controlled RCT of 3 days of nitazoxanide for the treatment of diarrhea and enteritis in children and adults from the Nile delta of Egypt, where *B. hominis* was the sole identified pathogen. Symptoms resolved 4 days after completing therapy in 36 (86%) of 42 patients who received nitazoxanide and 16 (38%) of 42 patients who received placebo (*p* < 0.0001). Thirty-six (86%) of 42 patients who received nitazoxanide were free of *B. hominis* organisms in each of three post-treatment stool samples compared with only 5 (12%) of 42 patients who received placebo (*p* < 0.0001). These findings suggest either that *B. hominis* is pathogenic in some patients and can be treated effectively with nitazoxanide or, alternatively, that nitazoxanide is effective in treating other unidentified causes of persistent diarrhea. Other agents that should be active against *Blastocystis* and also against likely occult pathogens such as *Giardia* are metronidazole, tinidazole, albendazole, and furazolidine.

**Cryptosporidium**

*Cryptosporidium parvum* infection causes frequent, watery diarrhea, without blood in immunocompetent children. Other prominent symptoms include crampy abdominal pain, fever, and vomiting. Asymptomatic infection is rare. Infections are often waterborne; the cysts are resistant to chlorine, and contaminated water and swimming pools have been the source of large outbreaks. In immunocompetent children, infection usually resolves after 10 days (range 1–20) and requires no specific treatment. Immunocompromised children can develop severe chronic diarrhea, which may be life-threatening. In patients with HIV infection, highly active antiretroviral therapy often reduces symptoms.
Immunocompetent patients tend to respond better to antiparasitic agents than immunocompromised patients for whom the agents are most needed. Trials have shown conflicting results. Paromomycin showed promise in a small RCT of HIV-infected patients, but a larger multicenter study found it was no better than placebo. In two studies of immunocompetent children with Cryptosporidium infection, spiramycin was found to have modest benefits in terms of shortening diarrhea and reducing oocyst excretion in one study, but no benefit in another study. Azithromycin improved symptoms in HIV-positive patients but did not prevent continued oocyst excretion. Nitazoxanide (see p. 82) shows most promise. In immunocompetent children, nitazoxanide reduces the duration of diarrhea and of oocyst excretion. In one study of immunocompetent children in Egypt, nitazoxanide reduced mortality (0 of 25 compared with 4 of 22 in the placebo group). The data are less clear-cut in HIV-infected patients, with some studies in adults showing benefit, while others, including a pediatric study, showed none.

We do not recommend treating immunocompetent children with Cryptosporidium diarrhea routinely, because treatment benefits are marginal at best and the disease self-limiting. In contrast, Cryptosporidium infection can be life-threatening in immunocompromised children. We recommend reducing immunosuppression, if possible. To treat Cryptosporidium in immunocompromised children, we recommend:

- nitazoxanide 1–3 years: 100 mg 12-hourly; 4–11 years: 200 mg 12-hourly; 12 years or older: 500 mg orally 12-hourly, for 3 days

**Giardiasis**

*Giardia lamblia* is a flagellate protozoan parasite with a worldwide distribution. Infection is primarily waterborne, and although humans are the main reservoir of infection, animals such as dogs and cats can contaminate water with infectious cysts. Infection can be asymptomatic, can be acute with watery diarrhea and abdominal pain, or prolonged with chronic or intermittent foul-smelling stools, abdominal distension, flatulence, and anorexia. Diagnosis is by detecting cysts in stool. Although ELISA tests on stool are slightly more sensitive than direct microscopy for ova and parasites, one study suggested that both tests need to be performed to achieve a sensitivity >90%. Immunofluorescent antibody testing of stool has also been claimed to be more sensitive than microscopy. Sensitivity of any of these tests is <95%, so that diagnosis in difficult cases may require examination of aspirated duodenal fluid.

There are few RCTs of treatment of acute or chronic giardiasis, and the outcome of trials is often reported as parasitologic rather than clinical cure. This is problematic, because most authorities agree that treatment of patients with asymptomatic passage of *Giardia* cysts is unwarranted. The traditional treatment of symptomatic patients is with metronidazole, which is 80–95% effective in clinical cure but has unpleasant adverse effects of nausea and unpleasant taste. In adult studies, tinidazole is at least as effective as metronidazole at curing symptoms and eradicating cysts and in one study was superior, and tinidazole has fewer reported adverse events. In one RCT in children, single-dose tinidazole was more effective than single-dose metronidazole and only minor adverse events were reported. In two RCTs in children, tinidazole was more effective than albendazole at eradicating cysts. Tinidazole is not licensed in the USA because of insufficient safety data in children. Furazolidone was as effective as metronidazole in one RCT. Albendazole was as effective as metronidazole in children in India and Turkey, but less effective in children than tinidazole in Indonesia and Chile. Nitazoxanide was as effective as metronidazole in Peruvian children.

For symptomatic patients, we recommend:

- tinidazole 50 mg/kg (max 2 g) orally, as a single dose OR
- metronidazole 5 mg/kg (max 250 mg) orally, 8-hourly for 5 days

Albendazole, furazolidone, and nitazoxanide are alternatives. Treatment failure is more common in immunocompromised children who may require prolonged treatment with one of the above agents or may need combinations of the above drugs. For immunocompetent children who fail therapy, it is usual to repeat the original course while investigating whether reinfection may have occurred from a family member or water source. There is no good evidence on this approach or on prolonging the treatment or increasing the dose.
Isospora belli gastroenteritis

*I. belli* usually causes gastroenteritis only in HIV-infected and other immunocompromised subjects. The clinical features resemble cryptosporidiosis. We recommend:

\[
\text{trimethoprim + sulfamethoxazole } 4 + 20 \text{ mg/kg (max } 160 + 800 \text{ mg)} \text{ orally, 6-hourly for 10 days}
\]

Long-term suppressive therapy with trimethoprim + sulfamethoxazole 4 + 20 mg/kg (max 160 + 800 mg) orally three times per week is generally required to prevent relapse in HIV-infected patients.\(^{144}\)

Microsporidium

Microsporidia such as *Enterocytozoon bieneusi* and *Encephalitozoon (Septata) intestinalis* can cause chronic diarrhea in immunocompromised patients, particularly HIV-infected patients, and the latter organism can disseminate. Microsporidia can also cause sub-acute diarrheal illness in immunocompetent children.\(^{145}\)

In an RCT, albendazole produced clinical improvement within 48 hours in 95% of immunocompetent children with chronic diarrhea (>10 days) due to Microsporidia.\(^{146}\)

We recommend:

\[
\text{albendazole } 10 \text{ mg/kg (max } 400 \text{ mg)} \text{ orally, 12-hourly for 7 days}
\]

7.12 Helicobacter pylori infection

Acute *H. pylori* infection can cause a self-limiting gastritis. Chronic *H. pylori* infection is an important cause of chronic active gastritis and of peptic ulcers in adults, but much less often in children. Children with recurrent abdominal pain and suspected gastritis or peptic ulceration can be screened non-invasively for *H. pylori* infection with a urea breath test. The \(^{13}\)C-urea breath test is a highly useful screening tool which was found in a large multicenter study to have sensitivity 96.2% and specificity 97.3% compared to endoscopically confirmed infection.\(^{147}\)

Although biopsy is often recommended to confirm the diagnosis by culture or histopathology, the urea breath test is so accurate that a case can be made for treating children with a positive urea breath test empirically and only doing a biopsy if they fail treatment.\(^{147}\)

Treatment is complicated by varying response rates, perhaps due to antibiotic resistance, which varies geographically. The standard triple therapy is a proton pump inhibitor (usually lansoprazole or omeprazole) plus amoxicillin plus clarithromycin for 10 days: this was 74% effective in eradicating the organism, compared to 9% spontaneous recovery in a large placebo-controlled RCT.\(^{148}\)

The benefits of susceptibility testing are debatable, but patients who do not respond to standard triple therapy often respond if metronidazole or tinidazole is used instead of clarithromycin.\(^{149,150}\)

An alternate proposal which improved efficacy to 97% in an RCT\(^{151}\) is to use 5 days of omeprazole plus amoxicillin followed by 5 days of omeprazole plus clarithromycin plus tinidazole.

7.13 Liver abscess

Liver abscesses in children are rare, particularly in industrialized countries. They are pyogenic, amebic (see p. 89), or hydatid (see p. 257). Pyogenic liver abscesses usually spread from an intra-abdominal source of infection, such as appendicitis. Abscesses can be single or multiple. Polymicrobial infections, with aerobic and anaerobic bowel flora are common, but occasionally an organism of the *Streptococcus anginosus/milleri* group may be found alone. In pediatric series, *Staphylococcus aureus* is a common isolate,\(^ {152,153}\) and so are Gram-negative enteric bacilli including *E. coli*\(^ {153}\) and *Klebsiella pneumoniae*.\(^ {154}\)

The latter organism is increasingly cultured from liver abscesses in adults in Asia.\(^ {155,156}\)

Children with pyogenic abscesses usually present with fever, abdominal pain, and an enlarged, tender liver.\(^ {152,153}\) Occasionally children will have fever without other signs or symptoms. Imaging is critical to make the diagnosis and for guided aspiration, which is important therapeutically and to distinguish pyogenic abscesses from abscesses due to ameba or hydatid disease. If aspiration cannot be done or amebic liver abscess or hydatid disease is suspected, we recommend serological testing for *Entamoeba. histolytica* (amoeba) and *Echinococcus granulosus* (hydatid).

For empiric treatment of pyogenic liver abscess, to cover *S. aureus*, anaerobic streptococci, and Gram-negative organisms, we recommend:

\[
\text{clindamycin } 10 \text{ mg/kg (max } 450 \text{ mg)} \text{ IV, 8-hourly PLUS}
\]

\[
\text{gentamicin } <10 \text{ years: } 7.5 \text{ mg/kg IV, daily;}
\]

\[
\text{10 years or older: } 6 \text{ mg/kg IV, daily}
\]
7.14 Hepatitis A

Hepatitis A virus is an RNA virus classified as a picornavirus (from pico = small + RNA). Infection can be asymptomatic. Symptomatic infection develops after an average incubation period of 28 days (range 15–50 days).\(^\text{157}\) Onset is typically abrupt with fever, malaise, anorexia, nausea, and abdominal discomfort, followed by dark urine and jaundice. The likelihood of infection causing symptoms is related to age. In children aged <6 years, 70% of infections are asymptomatic, and if illness does occur it is typically not accompanied by jaundice.\(^\text{158}\) In older children and adults, infection typically is symptomatic, with jaundice occurring in over 70% of patients.\(^\text{159}\) Signs and symptoms typically last up to 2 months, although 10–15% of symptomatic persons have prolonged or relapsing disease lasting up to 6 months.\(^\text{160}\) The overall case-fatality ratio in the USA is approximately 0.3–0.6%.\(^\text{161}\) There is no specific treatment for hepatitis A virus infection. However, hepatitis A infection can be prevented. Important preventive measures are active immunization with one of the inactivated hepatitis A vaccines or passive protection with human immunoglobulin. Hepatitis A vaccine is routine in some countries and is recommended for travelers to high-risk countries.

Prophylaxis of unimmunized family contacts with normal human immunoglobulin is recommended by public health authorities, and it is stated that normal human immunoglobulin contains enough antibodies against hepatitis A for post-exposure prophylaxis and short-term prophylaxis.\(^\text{161}\) What is the evidence?

**Question**  | For persons exposed to hepatitis A infection, does normal human immunoglobulin compared to no treatment or placebo prevent hepatitis A virus infection?

**Literature review**  | We found six RCTs and a non-Cochrane systematic review.\(^\text{162}\)

A non-Cochrane systematic review found six studies of variable quality and heterogeneity. Compared with placebo or no treatment, human immunoglobulin was 83% effective in primary prevention (RR 0.17, 95% CI 0.15–0.19) and 69% effective in prevention after exposure (RR 0.31, 95% CI 0.20–0.47).\(^\text{151}\) The average duration of passive protection was 3 months.\(^\text{162}\) Some of the variability may relate to when prophylaxis was given. Immunoglobulin is most effective in preventing symptomatic hepatitis A infection when administered early in the incubation period, although administration later in the incubation period can reduce the severity of infection.\(^\text{163}\) Normal human immunoglobulin is safe and has not transmitted other virus infections, such as hepatitis B or HIV.\(^\text{161}\)

The dose recommended for short-term protection (e.g., for an unimmunized traveler who is going to leave the country too soon to be fully immunized) and for post-exposure prophylaxis (for a family member of a person with hepatitis A) is:

normal human immunoglobulin 0.02 mL/kg, IM

Normal human immunoglobulin is no longer routinely recommended to protect travelers, because safe and effective killed vaccines are now readily available.

7.15 Hepatitis B

Hepatitis B virus (HBV) is a DNA virus that causes one of the commonest infections in the world. The most important antigens of HBV are the surface antigen (s), the core antigen (c), and the early antigen (e).

There are over 400 million persons chronically infected with HBV worldwide (carriers).\(^\text{164,165}\) Carriers of HBV have large amounts of infectious virus in their serum, as well as in their liver, but little or no antibody. This is referred to as being surface antigen positive or HBsAg positive. Chronic hepatitis B infection can progress to cirrhosis and liver cancer. The virus is responsible for more than 300,000 cases of liver cancer every year and for similar numbers of gastrointestinal hemorrhage and ascites. More than a quarter of all carriers with chronic hepatitis B will die of liver disease, and more than 1 million people with this infection die every year.\(^\text{164,165}\)

**Prevention of HBV infection**

**Routine immunization against hepatitis B**

Primary immunization of persons at birth or in adolescence with hepatitis B vaccine before exposure to HBV is at least 95% protective against infection.\(^\text{164–166}\) In many countries, both developing and industrialized, hepatitis B immunization is part of the primary childhood immunization schedule.
Management of baby born to mother who is an HBV carrier

Children can acquire HBV infection by mother-to-child transmission before or around the time of birth from their carrier mother (sometimes called “vertical infection”) or postnatally from exposure to the virus (“horizontal transmission”). In Southeast Asia, the vast majority of carriers are infected vertically (mother-to-child), while in contrast most children in Africa who become carriers acquire HBV horizontally.164,165

Perinatal transmission is believed to account for 35–50% of all hepatitis B carriers.165 If the mother is a chronic carrier (surface antigen positive), and particularly if she is e-antigen positive, which is a marker of infectivity (i.e., HBsAg and HBeAg positive), the risk of mother-to-child transmission is 70–90% without intervention.166,167 Studies have examined the use of hepatitis B vaccines, containing surface antigen purified from plasma or obtained by recombinant DNA technology, and hepatitis B immunoglobulin (immunoglobulin with a high titer against HBV) to prevent mother-to-child transmission.

**Question** | For babies born to hepatitis B carrier mothers, does hepatitis B vaccine plus immunoglobulin or vaccine alone or immunoglobulin alone compared with no treatment or placebo vaccine prevent mother-to-child transmission of HBV?

**Literature review** | We found 29 RCTs and a Cochrane review.168

A Cochrane review looked at the safety and efficacy of hepatitis B immunoglobulin and/or hepatitis B vaccine given at birth to the infants of HbsAg-positive mothers to prevent mother-to-child transmission of hepatitis B.168 The reviewers found 29 RCTs, of which 5 were considered of high quality. Only 3 trials reported inclusion of hepatitis B e-antigen-negative mothers. Compared with placebo or no intervention, hepatitis vaccine reduced hepatitis B transmission by 72% (RR 0.28, 95% CI 0.20–0.40). No significant difference in efficacy was found between recombinant vaccine versus plasma-derived vaccine or between high-dose versus low-dose vaccine. Compared with placebo or no intervention, hepatitis B immunoglobulin reduced hepatitis B transmission by 50% (RR 0.50, 95% CI 0.41–0.60). The combination of vaccine plus hepatitis B immunoglobulin was more effective than either alone. Vaccine plus hepatitis B immunoglobulin reduced hepatitis B occurrence by 92% compared with no intervention or placebo (RR 0.08, 95% CI 0.03–0.17, 3 trials).167

**We recommend giving hepatitis B vaccine plus immunoglobulin at birth to women who are carriers of hepatitis B.**

Mother-to-child transmission could occur transplacentally (intrauterine), peripartum, or post-natally from breast milk (carriers’ breast milk is known to contain live virus).163,164 The fact that most mother-to-child transmission can be interrupted by interventions at birth implies that most transmission occurs peripartum or post-natally rather than in utero. The only proviso is that HBV has a long incubation period (6 wk to 6 mo) and so it is possible that intrauterine infection could be altered by active and passive immunization at birth. Why does the baby not mount an immune response? The most likely explanation is that the baby’s immune system views the virus as “self” rather than foreign, and thus becomes “tolerant” of HBV. If they remain tolerant and unable to mount an immune response to the virus, this explains why later antiviral treatment is relatively ineffective at eradicating HBV from children who acquired HBV perinatally (see p. 94).

Even if hepatitis B immunization is part of the primary immunization schedule and the first dose is given at birth, it is still recommended to screen pregnant women for HBV status. This is because if they are HBeAg positive, their babies should be given immunoglobulin as well as vaccine at birth. If HBV vaccine is not in the primary immunization schedule, maternal screening is even more important.

The doses of vaccine and immunoglobulin vary from country to country. Prescribers should consult local guidelines.

**Post-exposure prophylaxis**

If an unimmunized child is accidentally exposed to hepatitis B or to a situation where there is a risk of hepatitis B, e.g., a needlestick injury, household, or sexual exposure, it is recommended to give hepatitis B immunoglobulin immediately and to start a course of hepatitis B vaccine (at 0, 1, and 6 mo) simultaneously.161 Because strong immunological memory persists more than 10 years after immunization of infants and adolescents with a primary course of vaccination, it is not considered necessary to give hepatitis B immunoglobulin or booster doses of
vaccine following accidental exposure,\textsuperscript{169} because evidence suggests that children will mount an anamnestic response and boost their antibody levels.\textsuperscript{170}

**Treatment of chronic carriers**

Carriers may be treated when they are asymptomatic to reduce their long-term risk of progressing to cirrhosis or they may need treatment because they have already started to develop liver disease, either symptomatic or discovered from liver function tests. Treatment of the former aims to induce seroconversion and clear HBV, while in the latter case treatment aims to improve liver function. The treatment of chronic carriers is complex, particularly children.

Adults may occasionally clear surface antigen spontaneously and start producing surface antibody. The proportion of adults seroconverting and clearing the virus can be improved by using antivirals, such as interferon-\(\alpha\) or lamivudine.\textsuperscript{171} Seroconversion is often associated with a transient rise in transaminases.\textsuperscript{163,164} Children who acquired HBV perinatally are far less likely to seroconvert than children who acquired HBV horizontally.\textsuperscript{172−175} This is presumably because perinatally infected children remain tolerant of the virus. A number of studies have shown that treatment of carrier children with interferon-\(\alpha\),\textsuperscript{172} lamivudine,\textsuperscript{173} interferon-\(\alpha\) plus lamivudine,\textsuperscript{174} or with interferon-\(\alpha\) plus steroids\textsuperscript{175} can improve liver function (reduced elevated liver enzymes, reduced viral load, and sometimes clearance of \(e\) antigen and production of \(e\) antibody). However, none of these regimens was associated with an increased rate of eradication of surface antigen; i.e., the children still remained carriers. For this reason, we do not recommend treating carriers who are well and whose liver enzymes are normal or near normal. Chronic carriers should be followed with regular clinical examination and liver function tests (enzymes, viral load, serology). If there is a sustained rise in liver enzymes to greater than twice normal, we recommend discussion with a pediatric gastroenterologist with a view to possible liver biopsy and treatment with antivirals.

**7.16 Hepatitis C**

More than 170 million people worldwide are chronically infected with hepatitis C virus (HCV), resulting in more than 100,000 cases of liver cancer per year and similar numbers of episodes of gastrointestinal hemorrhage and ascites.\textsuperscript{176} The combination of pegylated interferon and ribavirin can eradicate the virus in more than 50\% of patients.\textsuperscript{177,178} These antiviral treatments reduce liver fibrosis progression and can reverse cirrhosis. Although there are few studies in children, RCTs in children with chronic active hepatitis C show that a sustained response can be achieved in 36\% of children treated with interferon-\(\alpha\) alone\textsuperscript{179} and 46\% of children given interferon-\(\alpha\) plus ribavirin.\textsuperscript{180} Adverse reactions associated with interferon, notably fevers, arthralgia, malaise, and psychiatric problems, are common at any age but particularly in children, and often lead to dose modification or cessation of treatment.\textsuperscript{179,180} The treatment of chronic hepatitis C infection in children is specialized, and we recommend that it be undertaken in joint consultation between a pediatric gastroenterologist and a pediatric infectious disease specialist.

There is no vaccine against hepatitis C and human immunoglobulin contains no HCV antibodies, and so mother-to-child transmission of HCV is not preventable currently. The risk of perinatal transmission is about 5–10\%, and virtually occurs only if mother is HCV RNA positive at delivery.\textsuperscript{176} Co-infection with HIV increases the risk. In a study of HCV-infected children of HCV-positive mothers, babies were tested 3 days after birth using PCR on blood.\textsuperscript{179} At least a third and perhaps as many as a half of all children were infected in utero, and this implied that post-partum transmission was rare.\textsuperscript{181} Although low-titer HCV RNA can be detected in the breast milk of viremic mothers, there is no demonstrable increased risk of transmission from breast-feeding.\textsuperscript{181,182} One study suggested that Caesarean section might reduce transmission,\textsuperscript{183} but this has not been confirmed\textsuperscript{181} and Caesarean section is not currently recommended, even for viremic mothers.\textsuperscript{184}

We recommend to HCV-infected mothers that Caesarean section is not indicated and that it is almost certainly safe to breast-feed. All infants born to infected women should be screened for hepatitis C.

**7.17 Worms**

Worm infestation impairs growth and possibly intellectual function and there is limited evidence that the
treatment of children with helminth infestation improves growth.\textsuperscript{185,186} Albendazole, mebendazole, and thiacetazone are not recommended in children <6 months of age because of lack of safety data, but pyrantel is reported to be safe in this age group.

**Tapeworm (Echinococcus granulosus)**

The larval forms of *E. granulosus*, and in adults, *E. multilocularis*, can cause hydatid disease (see p. 257).

**Hookworm (Ancylostoma duodenale or Necator americanus)**

Albendazole is superior to mebendazole or pyrantel in the treatment of hookworm,\textsuperscript{187,188} although price and availability can be important issues. For the treatment of hookworm we recommend:

- **albendazole** 400 mg (child ≤10 kg but not <6 months old: 200 mg) orally, as a single dose OR mebendazole 100 mg (child ≤10 kg but not <6 months old: 50 mg) orally, 12-hourly for 3 days OR pyrantel 20 mg/kg (max 750 mg) orally, as a single dose (repeat after 7 days if heavy infection)

**Strongyloidiasis (Strongyloides stercoralis)**

For the treatment of strongyloidiasis in immunocompetent patients, ivermectin is superior to albendazole.\textsuperscript{189} We recommend:

- ivermectin 200 μg/kg (adult and child >5 years)
  orally, single dose OR
- albendazole 400 mg (child ≤10 kg: 200 mg)
  orally, daily for 3 days

Some authorities recommend repeating each course 1–2 weeks later, but an RCT suggested this is unnecessary and increases toxicity.\textsuperscript{190} Treatment is not always successful, especially in immunosuppressed patients, and may need to be repeated at monthly intervals or a longer course given.

**Pinworm or threadworm (Enterobius vermicularis)**

Pinworm and threadworm are common names for the same organism, *Enterobius vermicularis*. We found no RCTs of treatment, only observational studies. Drugs that have been shown in observational studies to be effective are:

- mebendazole 100 mg (child ≤10 kg: 50 mg) orally, as a single dose OR pyrantel 10 mg/kg (max 750 mg) orally, as a single dose OR albendazole 400 mg (child ≤10 kg: 200 mg) orally, as a single dose

**Whipworm (Trichuris trichiura)**

In an RCT of treatment of asymptomatic children with whipworm (trichuriasis), albendazole was more effective than pyrantel for children with heavy infestation, but the opposite was true if infestation was less severe.\textsuperscript{184} For the treatment of whipworm, we recommend:

- mebendazole 100 mg (child ≤10 kg: 50 mg) orally, 12-hourly for 3 days OR pyrantel 10 mg/kg (max 750 mg) orally, as a single dose OR albendazole 400 mg (child ≤10 kg: 200 mg) orally, daily for 3 days

**Community worm programs**

Age-targeted chemotherapy has been recommended because some overseas studies have found that treatment of helminth worm infestation improves nutrition and growth. A Cochrane review\textsuperscript{191} of 30 trials (>1500 children) found that a single dose of any anthelminth was associated with short-term weight gain of a mean of 0.17–0.38 kg. If repeat doses were given, there was a non-significant mean weight gain of 0.12 kg a year later. Results from studies of cognitive performance were mixed and inconclusive. Thus the benefits were marginal.

If it is decided to treat children aged 6 months to 12 years in a community where helminthic infections are endemic, the recommended treatment is:

- **albendazole** 400 mg (child ≤10 kg: 200 mg) orally, as a single dose every 4–6 months

**References**

36 Brown KH, Gastanaduy AS, Saavedra JM et al. Effect of continued oral feeding on clinical and nutritional outcomes


73 Panos GZ, Betsi GI, Falagas ME. Systematic review: are antibiotics detrimental or beneficial for the treatment of patients with *Escherichia coli* O157:H7 infection? *Aliment Pharmacol Ther* 2006;24:731–42.


130 Doumo O, Rossignol JF, Pichard E et al. Nitazoxanide in the treatment of cryptosporidial diarrhea and other intestinal


CHAPTER 8
HIV infection

The management of HIV infection in pregnancy, the management of babies born to HIV-infected mothers, and the management of children with post-natally acquired HIV infection are all highly specialized. There are regularly updated Web sites that provide detailed information on many aspects of the management of HIV infection in adults and children. Because of the complexity, we strongly recommend consultation with HIV experts when faced with difficult treatment decisions.

In this chapter, we will discuss the diagnosis of HIV infection, general principles about antiretroviral therapy, the prevention of mother-to-child transmission (MTCT) of HIV infection, and the management of potential needlestick or sexual exposure to HIV.

8.1 Clinical presentation of HIV infection in babies and children

HIV-infected infants and children may develop early acquired immunodeficiency syndrome (AIDS)-defining illness or can remain asymptomatic for years before developing an opportunistic infection. A bimodal distribution of perinatally infected infants has been described. Babies infected with HIV by MTCT can progress rapidly and present in the first few months of life with failure to thrive or severe malnutrition, diarrhea, persistent or recurrent oral candidiasis, or with Pneumocystis jiroveci (previously P. carinii) pneumonia (still called PCP). The classic presentation of PCP is with non-productive cough, fever, tachypnea, and dyspnea, increasing in severity over a period of 2–3 weeks. Oxygen saturation is often low, but cyanosis is a late sign. Children with PCP sometimes have a more fulminant presentation.

A minority of perinatally HIV-infected children are so-called slow progressors and may remain asymptomatic for years. Slow progressors may present with lymphoid interstitial pneumonitis (LIP), persistent or recurrent oral candidiasis, neurologic signs due to HIV encephalopathy, or with opportunistic infections, which are considered to be AIDS-defining illnesses, such as PCP, esophageal candidiasis, chronic or disseminated infections secondary to CMV, HSV, or VZV, tuberculosis (TB), atypical mycobacterial infections, chronic diarrhea due to Cryptosporidium or other intestinal parasites, and rarely with cerebral toxoplasmosis or cryptococcosis.

Children who are perinatally infected despite receiving antiretroviral therapy progress slower than untreated children. Children with LIP may also develop hepatosplenomegaly, generalized lymphadenopathy, bilateral parotitis, and finger clubbing. This presentation can be difficult to distinguish from TB and also from disseminated Kaposi sarcoma, both of which occur in association with childhood HIV infection in Africa. Other common presenting features in HIV-infected children in Africa are chronic fever, recurrent pneumonia, and chronic dermatitis. TB, including neonatal TB and miliary TB in older children, is common in HIV-infected children in many developing countries.

It is relatively rare for HIV-infected children to develop malignancy. Tumors represent about 2% of the AIDS-defining events in children in the USA, most commonly non-Hodgkin lymphoma and smooth muscle tumors, although the incidence of Burkitt lymphoma is also increased in HIV infection. In Africa, children may present with dark lesions of the palate, gums, and skin and with lymphadenopathy and hepatosplenomegaly due to Kaposi sarcoma, and this clinical picture may be difficult to distinguish from TB.

HIV-infected persons started on highly active antiretroviral therapy (HAART) may develop exacerbations of preexisting chronic infections as a consequence of restoration of the immune response. These diseases are called immune reconstitution syndrome (IRS) or immune reconstitution inflammatory syndrome or
immune restoration diseases. They have been described mainly in adults. In Thailand, 19% of children developed immune reconstitution diseases over a median of 4 weeks (range 2–31) after starting HAART. Mycobacterial infections, due to Mycobacterium tuberculosis, BCG, or atypical mycobacterial infection, were the commonest diseases and presented with discharging lymph nodes, skin abscesses, or pulmonary infection. Other manifestations of IRS in these children were classic zoster, HSV infections (mostly herpes labialis but one child had HSV encephalitis), and recurrence of cryptococcal meningitis. IRS is being increasingly reported in children in industrialized countries.

8.2 Diagnosis of HIV infection in babies and children

There are various tests that are or have been used to diagnose HIV infection (see Table 8.1).

**Question** | For a baby or child with suspected HIV infection, which tests are sensitive and specific enough to be used to make a reliable diagnosis of HIV infection?

**Literature review** | We found a non-Cochrane meta-analysis comparing viral culture with antigen detection and clinical examination. We found 32 studies and a non-Cochrane meta-analysis of polymerase chain reaction (PCR) testing in infants and children. We found 5 studies comparing DNA PCR with RNA PCR.

**HIV viral antigen**

In the early days of testing for HIV infection in babies, HIV antigen detection was used as a rapid diagnostic assay when culture was unavailable or too slow and antibodies were likely to be maternal. The most useful antigen was the viral capsid protein antigen, p24. However, the test is not as sensitive as viral culture and has been superseded by molecular techniques.

**Viral culture**

In the first 6 months of life, viral culture is more sensitive for detecting HIV infection than physical examination, serum immunoglobulin determination, or HIV p24 antigen determination. Viral culture is slow and expensive and PCR techniques have made viral culture less essential. Viral culture is still useful for determining sensitivities to antiretrovirals and for serotyping HIV, so we recommend performing viral culture if virus is detected by PCR.

**HIV IgG antibodies**

Serum IgG antibodies specific to HIV are present in all HIV-infected persons. The only exceptions are immunocompromised persons who become so hypogammaglobulinemic that they have lost HIV antibodies and acutely infected subjects in the “window period” before they mount an immune response. For a child over 18 months old with suspected HIV infection, an HIV ELISA is the recommended test of choice to screen cheaply for HIV infection. If the ELISA is positive and there is sufficient serum left, the laboratory will repeat the ELISA and perform a Western blot assay to

Table 8.1 Tests for HIV infection.

<table>
<thead>
<tr>
<th>Category</th>
<th>Test</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV antigen</td>
<td>Serum HIV p24 antigen</td>
<td>No longer used due to low sensitivity³</td>
</tr>
<tr>
<td>Virus</td>
<td>HIV viral culture</td>
<td>Sensitive, but slow and costly</td>
</tr>
<tr>
<td>HIV IgG antibodies</td>
<td>ELISA test, confirmed with Western blot assay</td>
<td>Transplacentally acquired maternal IgG antibody persists for up to 18 months</td>
</tr>
<tr>
<td>HIV IgM antibodies</td>
<td>ELISA test</td>
<td>Unreliable and not commercially available³</td>
</tr>
<tr>
<td>HIV DNA</td>
<td>HIV DNA PCR</td>
<td>Sensitive and specific test for diagnosing HIV infection in child &lt; 18 months old¹⁶–⁴³</td>
</tr>
<tr>
<td>HIV RNA</td>
<td>HIV RNA PCR</td>
<td>Recent papers suggest at least as sensitive as DNA PCR³</td>
</tr>
</tbody>
</table>

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look for antibodies to different HIV antigens. Transplacently acquired maternal IgG antibody persists for up to 18 months, and so detecting HIV IgG antibodies in a child <18 months old does not distinguish an HIV-infected from an uninfected child.\(^1\)\(^3\)\(^8\)

**HIV IgM antibodies**
Attempts to develop serum IgM assays for HIV have been unsuccessful, and there is no reliable commercial HIV IgM test available.

**PCR tests for diagnosis of HIV**
A meta-analysis of 32 studies on PCR testing of infants and children\(^2\)\(^4\) found that the median sensitivity for diagnosing HIV infection was 91.6% (range 31–100%) and the median specificity was 100% (range 50–100%). The joint sensitivity and specificity was significantly higher in older infants (98.2%) than in neonates (93.3%). When there was a low risk of perinatal transmission (probability of transmission 8.3%), the positive predictive value for PCR was 55.8% in neonates (so almost half of the positive PCR tests were false positives) and 83.2% in older infants. A negative PCR result reduced the probability of HIV infection to less than 3%.

**HIV DNA PCR**
DNA PCR identifies 25–45% of HIV-infected babies in the first week of life, rising to over 90% by 14 days of age, and 95–100% by 2 months old.\(^18\)\(^–\)\(^23\) The sensitivity is high, 95–100%, although specificity may be decreased by false positives due to contamination.\(^18\)\(^–\)\(^23\) HIV DNA is more sensitive than HIV viral culture,\(^18\) as well as easier and cheaper to perform.

**HIV RNA PCR**
RNA PCR can be used as a qualitative test (detected or not detected) or as a quantitative test (how much RNA is detected). Like DNA PCR, RNA PCR is highly sensitive and specific. The term “quantitative RNA PCR” means the same as “viral load.” The sensitivity of RNA PCR for detecting HIV infection is 29–47% in the first week, rising to 78% at 8–28 days, and 95–100% by 2 months old.\(^20\)\(^–\)\(^23\),\(^25\)\(^–\)\(^27\)

We found five studies comparing sensitivity and specificity of DNA PCR and RNA PCR.\(^21\)\(^–\)\(^23\),\(^25\)\(^–\)\(^26\) One study reported no difference,\(^26\) while the others reported marginally better sensitivity in the first week of life for RNA PCR compared with DNA PCR, but no difference thereafter.\(^21\)\(^–\)\(^23\),\(^25\)

PCR techniques are sensitive and specific, quick, and relatively cheap.\(^8\) Although they are the best available tests for diagnosis of HIV infection in neonates and infants, the results are not definitive and should be interpreted with the aid of careful clinical follow-up examinations.

We recommend using either RNA PCR or DNA PCR to diagnose HIV infection in the first 18 months of life. After 18 months, we recommend HIV antibody testing by ELISA, confirmed by Western blot and PCR.

### 8.3 Antiretroviral therapy

**When to start HAART**
HAART has been associated with a significant fall in mortality from HIV infection, in rate of progression to AIDS,\(^28\)\(^–\)\(^29\) and in incidence of opportunistic infections.\(^30\)

There is no controversy that a child with AIDS should be started on HAART if it is available.\(^1\)\(^–\)\(^3\) However, there are issues of adherence, adverse effects of HAART, and drug interactions. There is no good evidence that starting all asymptomatic HIV-infected children on HAART improves survival, and there is at least a theoretical risk that starting HAART earlier might increase the risk of selecting for resistant HIV strains.

In a non-Cochrane meta-analysis of 3941 children from Europe and the USA, CD4 T-cell percentage (CD4%) was found to be more reliable than viral load in predicting death or progression to AIDS.\(^31\) CD4% was more reliable than absolute CD4 count in younger children. The risk of death increased sharply when CD4% was less than about 10%. The risk of AIDS increased when CD4 was <15%. The risk of progression increased when viral load exceeded about 10\(^5\) copies/mL, although this association was more gradual compared with CD4%.

In another non-Cochrane meta-analysis, CD4 count was a more reliable predictor of outcome than CD4% or viral load.\(^32\) The estimated risk of disease progression in children older than 4 or 5 years increased sharply when the CD4 cell count fell below 200–300 cells/µL. As with other immunologic markers, CD4 cell count was less prognostic in younger children.\(^32\)

We conclude that for asymptomatic HIV-infected children >4 years old, it is reasonable not to start HAART unless the child develops a significant
opportunistic infection or an AIDS-defining illness or until the CD4 count falls rapidly or falls below 300 cells/μL, or CD4% falls below 15%.

Before effective antiretroviral therapy was available, about 20% of infants in industrialized countries developed AIDS and 10% died within the first year of life.33–36 HAART has been associated with a significant fall in mortality in HIV-infected infants.37–39 HIV-1 RNA and CD4 count and percentage are poor predictors of disease progression and of death during infancy,31,32,37 which makes it more difficult to predict outcome for infants. There is some controversy whether or not all asymptomatic perinatally infected infants should be started immediately on antiretroviral therapy, for the same concerns expressed for older asymptomatic children.37 A French group has reported encephalopathy in untreated but not in treated infants.38 Treated infants in the French and in an American population-based cohort,39 but not in the British cohort,37 were reported to be less likely to progress to AIDS. Currently, most authorities recommend considering starting antiretroviral therapy for all infected children in the first year of life. We feel the evidence is not conclusive and are unable to make a firm recommendation.

Antiretroviral therapy

There are three major classes of antiretrovirals:

• The nucleoside or nucleotide analogue reverse transcriptase inhibitors (NRTIs) contain a molecule such as thymidine that mimics a nucleotide or nucleoside and thus inhibits the activity of the HIV reverse transcriptase enzyme necessary for HIV replication.

• The non-nucleoside reverse transcriptase inhibitors (NNRTIs) act in different ways from NRTIs, but also block reverse transcriptase.

• The protease inhibitors (PIs) act on the protease enzyme of HIV. A boosted PI is one used with a small dose of the PI ritonavir, resulting in a far higher concentration of the active drug.40–42

Other active drugs include the fusion inhibitors (FIs) such as enfuvirtide that prevent infection by blocking fusion of HIV to the CD4 T lymphocyte.

Integrate inhibitors are currently in development. Fixed drug combinations of two antiretroviral drugs in one tablet are increasingly available. Examples are zidovudine+lamivudine, lamivudine+abacavir, and emtricitabine+tenofovir. They may improve adherence, but allow less flexibility in dosing for children.

The antiretroviral drugs commonly used in children are shown in Table 8.2.

The recommended doses of antiretrovirals are sometimes expressed by weight (dose/kg) and sometimes by surface area (dose/m²). This reflects the sad lack of pharmacokinetic data in children. Because recommendations change frequently, we have not given doses but advise consulting one of the regularly updated Web sites.1–3 In addition, the Web site should be consulted for adverse drug reactions associated with each drug. We recommend that antiretrovirals should not be started or changed without expert consultation.

Antiretroviral drugs and drug interactions

The PIs and NNRTIs inhibit or induce the cytochrome P450 enzymes and interact with many other drugs. For example, rifampin (rifampicin) should not be used with any of the NNRTIs or PIs except efavirenz.

A comprehensive, up-to-date interaction Web site maintained by the University of Liverpool (UK) can be found at www.hiv-druginteractions.org/.

Antiretroviral combinations

Question | For HIV-infected children being treated with antiretroviral therapy, are three or four antiretroviral drugs more effective than one or two?

Literature review | We found three studies and a Cochrane review.43

A Cochrane review compared HIV maintenance regimens using three or four antiretrovirals with regimens using fewer drugs.43 Four trials were identified including three published studies and one abstract, all in adults. Compared to three- or four-drug maintenance therapy, maintenance therapies including fewer drugs were associated with a higher risk of virologic failure (loss of HIV suppression to non-detectable levels). Combining the results of all four studies yielded an OR for treatment failure of 5.6 (95% CI 3.1–9.8).41 Maintenance regimens of zidovudine and lamivudine compared to maintenance regimens with zidovudine, lamivudine, and indinavir were associated with significantly higher rates of virologic failure. Similarly, maintenance regimens that discontinued one or more PI after including them in induction therapy were also
Table 8.2 Antiretroviral drugs used in children.

<table>
<thead>
<tr>
<th>Class of Drug</th>
<th>Examples</th>
<th>Toxicity (Class Effect)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>Abacavir (ABC)*&lt;br&gt;Didanosine (ddI)&lt;br&gt;Emtricitabine (FTC)&lt;br&gt;Lamivudine (3TC)&lt;br&gt;Stavudine (d4T)&lt;br&gt;Tenofovir (TDF)&lt;br&gt;Zalcitabine (ddC)&lt;br&gt;Zidovudine (AZT, ZDV)</td>
<td>Class effect: lactic acidosis, hepatic steatosis, lipodystrophy</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Efavirenz (EFV)&lt;br&gt;Nevirapine (NVP)</td>
<td>Class effect: rash (including Stevens–Johnson syndrome), abnormal liver function, fever</td>
</tr>
<tr>
<td>PI</td>
<td>Nelfinavir (NFV)</td>
<td>Class effect: lipodystrophy (abnormal fat accumulation with central obesity, breast enlargement, buffalo hump or lipoatrophy (fat wasting in limbs and face), hyperglycemia, hyperlipidemia, abnormal liver function</td>
</tr>
<tr>
<td>Boosted PI</td>
<td>Atazanavir/ritonavir&lt;br&gt;Saquinavir/lopinavir/ritonavir&lt;br&gt;Tipranavir/ritonavir</td>
<td>Class effect: lipodystrophy (abnormal fat accumulation with central obesity, breast enlargement, buffalo hump or lipoatrophy (fat wasting in limbs and face), hyperglycemia, hyperlipidemia, abnormal liver function</td>
</tr>
<tr>
<td>FI</td>
<td>Enfuvirtide (T20)</td>
<td>Injection site reactions, hypersensitivity, increased incidence of bacterial pneumonia</td>
</tr>
</tbody>
</table>

*Potentially fatal hypersensitivity reactions develop in first 6 weeks in 5% of children on abacavir: fever, fatigue, malaise, nausea, vomiting, diarrhea, abdominal pain, dyspnea: stop drug and do not reintroduce.

associated with a significantly higher risk of virologic failure.43

The usual combination for initial antiretroviral therapy is:

**Two NRTIs plus one NNRTI OR**

**Two NRTIs plus one boosted PI**

The choice of when to start antiretroviral therapy (see p. 104) and which antiretroviral drugs to use is complex and we strongly recommend expert input.

### 8.4 Prophylaxis against PCP

Co-trimoxazole (trimethoprim-sulfamethoxazole, TMP-SMX) is effective chemoprophylaxis against pneumonia due to *P. jiroveci* (PCP) in immunocompromised persons when given daily, or thrice weekly.45 A Cochrane review found only one RCT of TMP-SMX prophylaxis in HIV-infected children in Zambia.47 The study showed a 33% reduction in mortality in children given prophylaxis. African adults given co-trimoxazole have similar reductions in mortality.48 We found no RCTs in industrialized countries.

HIV-infected children who are significantly immunocompromised are at highest risk of PCP, and TMP-SMX prophylaxis is indicated. The current recommendations state that these are children aged 1–5 years old with CD4 counts <500 cells/μL (<500 × 10⁹ cells/L) or children >5 years old with CD4 counts <200 cells/μL (<200 × 10⁹ cells/L).49,50 The current US guidelines also recommend giving TMP-SMX to all HIV-exposed babies aged 4 weeks to 4 months and to babies aged 4–12 months with indeterminate status.49 Because of the very low risk of transmission (<1%) when MTCT prevention measures have been taken (see Section 8.8, p. 108), this policy will expose a large number of children to TMP-SMX for little return.

The sensitivity of PCR tests is so high that we recommend stopping TMP-SMX prophylaxis at 3 months if an exposed baby is well and all tests including PCR tests are consistently negative.

In contrast, breast-fed babies in developing countries are at ongoing risk of catching HIV from breast milk, and the WHO recommends they are given
8.5 Immunization of HIV-infected children

Children with HIV infection who are immunocompromised will not mount as good an immune response to immunization (reduced T-helper cells leading to reduced cell-mediated immunity and reduced antibody production). In addition, they may be at risk of disseminated disease from live viral vaccines, such as measles vaccine, or from live bacterial vaccines, such as BCG. Indeed, there has been a case report of an adult with HIV who died from pneumonitis due to measles vaccine, and rare but potentially fatal cases of disseminated atypical mycobacterial disease (BCGosis) with BCG vaccine. Varicella vaccine is safe and immunogenic in HIV-infected children who are not immunocompromised. Vaccine recommendations vary with the child’s immune status and also with the child’s country of origin, which determines risk of exposure. Our current recommendations are given in Table 8.3.

8.6 Treating opportunistic infections

The treatment of opportunistic infections is dealt with in different chapters in this book. Expert recommendations on managing opportunistic infections in children are available from Centers for Disease Control and Prevention (CDC) and in guidelines.

8.7 Additional management issues for HIV-infected children and adolescents

There are many other management issues, in addition to giving antiretroviral drugs and monitoring for toxicity. These include to:

- counsel the child and the parents about the disease and the treatment;
- screen family members and contacts for infection, after counseling, and as appropriate;
- provide patient support and educational interventions (found by a Cochrane review to improve adherence to antiretroviral therapy);
- deal with ongoing psychosocial issues for the child and family;
- deal with school issues;
- educate adolescents about condom use (found by a Cochrane review to reduce heterosexual transmission of HIV by 80%).

### Table 8.3 Recommendations on immunization of HIV-infected children.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Industrialized Country, Asymptomatic</th>
<th>Industrialized Country, Symptomatic</th>
<th>Developing Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG</td>
<td>No</td>
<td>No</td>
<td>Yes, at birth</td>
</tr>
<tr>
<td>DTP</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Yes</td>
<td>Yes</td>
<td>Not usually available</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hib</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, if available</td>
</tr>
<tr>
<td>Influenza (inactivated)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, but not usually available</td>
</tr>
<tr>
<td>Measles or MMR</td>
<td>Yes</td>
<td>Yes, unless severely immunocompromised*</td>
<td>Yes</td>
</tr>
<tr>
<td>Meningococcal</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, if available</td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, if available</td>
</tr>
<tr>
<td>Polio vaccine</td>
<td>IPV</td>
<td>IPV</td>
<td>OPV</td>
</tr>
<tr>
<td>Varicella</td>
<td>Yes67</td>
<td>No</td>
<td>Not usually available</td>
</tr>
</tbody>
</table>

* Defined as CD4 count <750 cells/μL if <12 months, <500 aged 1–5 years, <200 aged >5 years.
Modified from References 52–54.
8.8 Prevention of MTCT of HIV infection

The risk of MTCT of HIV infection in the era before the use of antiretrovirals and other interventions to reduce transmission ranged from 13% in Europe\textsuperscript{61} to 45% in Africa.\textsuperscript{62} With the advent of maternal screening, HAART, bottle feeding, and caesarean section, the rate of transmission has fallen to <1% in industrialized countries.\textsuperscript{63,64}

**Question** | For pregnant women with HIV infection, does giving antiretrovirals to mother and/or baby compared with no treatment reduce MTCT of HIV infection? What is the most effective regimen? For pregnant women with HIV infection, does caesarean section compared to normal vaginal delivery reduce the risk further? For babies born to HIV-infected mothers, does bottle feeding compared to breast-feeding reduce the risk of HIV infection?

**Literature review** | We found a Cochrane systematic review\textsuperscript{65} and a more recent Clinical Evidence review\textsuperscript{66} of interventions to reduce MTCT of HIV. We found 15 RCTs on the use of antiretrovirals. We found 1 RCT on caesarean section. We found observational studies on bottle feeding.

**Antiretrovirals to prevent MTCT of HIV infection**

Early studies before the HAART era showed that monotherapy with zidovudine to treat mother and baby reduced MTCT of HIV infection. The seminal PACTG 076 study\textsuperscript{67} showed that treating mother and baby with zidovudine (AZT) compared with placebo reduced the rate of MTCT from 25.5 to 8.3%. Such studies were important to show effectiveness, but the regimens have been superseded. In industrialized countries, more effective regimens using HAART to treat HIV-infected women during pregnancy have reduced the risk of transmitting HIV to the baby to <1%. In developing countries, novel cheap and effective regimens can reduce the transmission rate to <2% (see Combination regimens, below).

**Zidovudine monotherapy**

Based on four trials (1585 women), any zidovudine regimen giving zidovudine to mother and baby significantly reduces the risk of MTCT compared with no treatment or placebo (OR 0.46, 95% CI 0.35–0.60).\textsuperscript{65,66} Zidovudine is also associated with a decreased risk of infant death within the first year (OR 0.57, 95% CI 0.38–0.85) and a decreased risk of maternal death (OR 0.32, 95% CI 0.16–0.66).

**Nevirapine**

The HIVNET 012 study of 626 women from a predominantly breast-feeding population in Uganda compared zidovudine with nevirapine.\textsuperscript{68} Nevirapine, given to mothers as a single oral dose at the onset of labor and to infants as a single dose within 72 hours of birth, significantly reduced the incidence of HIV infection at 14–16 weeks to 15% compared to 26% with oral zidovudine given to women during labor and to their newborns for 7 days after birth (RR 0.58, 95% CI 0.40–0.83).\textsuperscript{68}

There are some concerns about maternal hepatotoxicity from nevirapine. A case series from Ireland reported that 8 of 123 women given nevirapine as part of combination antiretroviral therapy during pregnancy developed significant hepatotoxicity, and 2 of them died from fulminant hepatitis.\textsuperscript{69} However, large RCTs have not reported increased hepatotoxicity or mortality in mothers and babies taking nevirapine compared with other regimens.\textsuperscript{65,70–73}

**Zidovudine plus lamivudine**

We found one RCT, the Petra study, that compared zidovudine+lamivudine with placebo in 1797 predominantly breast-feeding women in South Africa, Uganda, and Tanzania.\textsuperscript{70} Antiretroviral drugs given in the antenatal period (from 36 weeks), intrapartum, and post-partum (to mother and baby for 1 week) significantly reduced the risk of HIV transmission at 6 weeks to 5.7% compared with 15.3% in controls (RR 0.37, 95% CI 0.21–0.65).

**Combination regimens**

The most impressive results in developing country are from Thailand.\textsuperscript{74} In a large RCT of 1844 non-breast-feeding women, a regimen of zidovudine from 28 weeks gestation plus a single dose of nevirapine to mothers and a single dose of nevirapine at birth followed by 1 week of zidovudine to babies reduced the transmission rate at 6 months to 2%.\textsuperscript{74}
Recommendations on antiretrovirals for newborn babies

Recommendations on antiretroviral treatment for babies are complicated and depend on circumstances such as the mother’s antiretroviral therapy, her HIV viral load, mode of delivery, and breast- or bottle feeding. Advice is available from Web sites such as the US Department of Human Health and Services Web site (http://aidsinfo.nih.gov/guidelines/) and is regularly updated. If in doubt, consult a specialist.

The US recommendations at the time of writing refer to four clinical scenarios. We have modified these scenarios into situations that we feel clinicians are likely to face in current practice. We have given the doses of antiretrovirals for full-term babies. For preterm babies, see below.

Scenario 1: Pregnant mother, no prior antiretroviral therapy, has detectable virus

We recommend starting the mother on HAART.

The recommendation for the baby will depend on whether or not the mother has detectable virus at delivery (see Scenarios 2 and 3).

Scenario 2: Mother in labor, already on HAART, no detectable virus

A collaborative European and US study of mothers with viral load <1000 copies/mL found that the transmission rate to babies of mothers taking antiretrovirals was 1% compared with 9.8% for mothers not taking antiretroviral treatment.75 If the mother was treated with antiretrovirals, her newborn usually was, too.75 For this reason, we recommend treating mothers with no detectable virus and their babies using antiretrovirals. The regimen used is debatable because of lack of data. One of the concerns is toxicity because antiretrovirals given to the mother are sometimes associated with mitochondrial damage in babies.76 It would not be unreasonable to give three antiretrovirals, as in Scenario 4 below. However, as a balance between risk and benefit, we currently recommend only zidovudine, a drug that has been shown in a meta-analysis to halve the risk of transmission.65 For the baby, we recommend:

zidovudine (AZT) syrup 4 mg/kg orally,
12-hourly for 6 weeks

The British HIV Association (BHIVA) guidelines, however, recommend giving the baby triple therapy in this situation, based on expert opinion.

Scenario 3: Mother in labor, already on HAART, has detectable virus

This situation suggests probable resistance to antiretrovirals and/or non-adherence and is complex. We recommend seeking expert advice.

Scenario 4: Mother in labor, no prior antiretroviral therapy, has detectable virus

The optimum therapy has not been proven, but because of the high risk to the baby when mother has detectable virus at delivery and the proven efficacy of three-drug regimens,43 we recommend giving IV zidovudine to the mother followed by treatment of the baby with:

zidovudine (AZT) syrup 4 mg/kg orally
12-hourly for 6 weeks PLUS
lamivudine (3TC) syrup 2 mg/kg orally,
12-hourly for 6 weeks PLUS
nevirapine syrup 2 mg/kg single dose orally at 48–72 hours old

The BHIVA guidelines recommend 4 weeks of antiretrovirals for the baby, based on expert opinion.

Antiretroviral drug doses for preterm babies

For preterm babies >30 weeks gestation at birth (if they can tolerate oral therapy), the dose is:

zidovudine (AZT) syrup 2 mg/kg orally,
12-hourly for 2 weeks, THEN
zidovudine (AZT) syrup 2 mg/kg orally, 8-hourly for 4 weeks

For babies unable to take oral medication, zidovudine (AZT) is the only IV antiretroviral available. Change to the oral dosage as soon as one can tolerate oral feeds. We recommend:

>34 weeks gestation at birth: zidovudine (AZT)
1.5 mg/kg IV, 6-hourly
30–34 weeks gestation at birth: zidovudine (AZT)
1.5 mg/kg IV, 12-hourly for 2 weeks THEN
zidovudine (AZT) 1.5 mg/kg IV, 8-hourly, from 2 to 6 weeks of age
<30 weeks gestation at birth: zidovudine (AZT)
1.5 mg/kg IV, 12-hourly for 4 weeks THEN
zidovudine (AZT) 1.5 mg/kg IV, 8-hourly, from 4 to 6 weeks of age

There is no dose adjustment of lamivudine (3TC) or nevirapine for preterm infants.
The BHIVA guidelines recommend 4 weeks of antiretrovirals for the baby, based on expert opinion.

**Caesarean section**

There is only one RCT comparing elective caesarean section with anticipation of vaginal delivery. This European study was in the pre-HAART era and involved 436 participants. Caesarean section significantly reduced the risk of MTCT of HIV infection to 1.8% compared with 10.5% with vaginal delivery (RR 0.17, 95% CI 0.05–0.55).

Two Cochrane systematic reviews found no RCTs of caesarean section since HAART was used. They found, however, that maternal post-partum morbidity was greater with elective caesarean section than with vaginal delivery, although morbidity is greater still with emergency caesarean section.

Post-partum morbidity rates for HIV-1-infected women have declined over time, suggesting that the risk of post-partum morbidity with elective caesarean section is decreasing as the medical (antiretroviral therapy) and surgical (peripartum antibiotic prophylaxis) management of HIV-1-infected women improves.

The benefit of elective caesarean section delivery is unclear for HIV-1-infected women with less advanced or well-controlled HIV-1 disease whose risk of MTCT is extremely low (<2%). In such a setting, the short-term risk of the intervention (i.e., morbidity experienced by the mother within the first 6 weeks after delivery) may exceed the rare but important long-term benefit (prevention of HIV-1 transmission to the infant). For women with poorly controlled HIV-1 disease and/or no antiretroviral prophylaxis or treatment, the benefit of elective caesarean section generally outweighs the risk of maternal morbidity.

Obstetric HIV-1-infected women with a very low risk of transmission to infants, irrespective of mode of delivery, should be individualized after discussion between the woman and her obstetrician.

**Breast-feeding**

Most data on the risk of HIV transmission through breast-feeding come from non-randomized observational studies in developing countries. An early meta-analysis estimated that if a baby born to an HIV-infected mother was not infected at birth, there was a 14% additional risk of post-natal transmission from breast-feeding. The risk for babies born to women who developed HIV infection post-partum was higher at 29%, presumably because the latter women were more viremic.

A review found that the cumulative probability of late post-natal transmission was 9.3% by 18 months, and the overall risk of late post-natal transmission was 8.9 transmissions/100 child-years of breast-feeding.

Early mixed bottle- and breast-feeding is associated with a fourfold increased risk of HIV transmission compared with breast-feeding alone. This may be because cow’s milk causes mucosal damage.

There has been only one intervention study, an RCT from Kenya in which children born to 425 HIV-infected women were randomized to breast-feeding or replacement feeding. The results showed that 44% of infant HIV infections were acquired through breast-feeding and that most infections were acquired during the first few months of life. The cumulative probability of HIV-1 infection at 24 months was 36.7% in the breast-feeding arm and 20.5% in the formula arm (p = 0.001), giving an estimated rate of breast milk transmission of 16.2% (95% CI 6.5–25.9%). Most breast milk transmission occurred early, with 75% of the risk difference occurring by 6 months, although transmission continued throughout the duration of exposure. The 2-year mortality rate was similar in both arms (breast-feeding 24.4% versus formula feeding 20.0%, p = 0.30). At 2 years, babies in the breast-feeding arm were less likely to be free of HIV infection (58.0%) than babies in the formula feeding arm (70.0%, p = 0.02). This RCT casts doubt on the WHO recommendation that women in developing countries should breast-feed because bottle feeding is more dangerous.

Although the WHO and others have traditionally recommended that women in developing countries should breast feed, because the risk of diarrheal and other diseases attributable to formula feeding outweighs the risk of contracting HIV, this rule no longer seems to be generally applicable. Current data suggest that in some African countries, the risk of breast-feeding may be greater than the risk of formula feeding. An alternative which is being investigated in some countries is to use pasteurized (heat-treated) expressed breast milk to feed babies, but
it seems unlikely that this will be practical in resource-poor settings.

In industrialized countries, HIV-infected women should be advised to feed their babies with formula and not to breast feed.

8.9 Post-exposure prophylaxis against HIV infection

Post-exposure prophylaxis against HIV infection should be considered following exposure to a person known to be HIV-infected or when the person may be HIV-infected but their HIV status is unknown. The common routes of exposure are from needlestick injuries in health care or associated with IV drug-using equipment, sexual exposure, or breast milk.

Question | For persons exposed to HIV infection, does antiretroviral therapy compared with no treatment or placebo reduce the risk of acquiring HIV infection?

Literature review | We found a non-Cochrane systematic review of the risk of infection following parenteral exposure to HIV.88 We found a non-Cochrane systematic review of post-exposure prophylaxis for non-occupational exposure to HIV.89 We found guidelines on post-exposure prophylaxis for adults90,91 and children.89

A review of post-exposure prophylaxis found no RCTs.89 A case-control study from the USA and Europe evaluated 33 health-care workers who acquired HIV infection after occupational exposure and 679 controls who did not acquire HIV infection after 6 months follow-up despite occupational exposure.92 After adjustment for confounding factors, people who had acquired HIV infection were less likely to have taken post-exposure prophylaxis with zidovudine than the controls who had not acquired HIV (adjusted OR 0.19, 95% CI 0.06–0.52, p = 0.003).

We found no controlled studies of post-exposure prophylaxis using combinations of antiretrovirals and no studies of the efficacy of post-exposure prophylaxis in the community outside the health-care setting.

Zidovudine prophylaxis is associated with adverse events such as fatigue, nausea, vomiting, and gastrointestinal discomfort in 50–75% of health-care workers and about 30% of them stop taking post-exposure prophylaxis.92 The frequency of reported adverse effects (50–90%) is higher in people taking a combination of antiretroviral drugs, so multidrug prophylaxis might reduce adherence to post-exposure prophylaxis.93 Adverse effects are rarely severe or serious, and even severe adverse events are transient.93

Risk of acquiring HIV from exposure

A systematic review of transmission risks quantified the risk of acquiring HIV, which varies according to the nature of the exposure.89 The results are summarized in Table 8.4.

<table>
<thead>
<tr>
<th>Nature of Exposure</th>
<th>Risk of Acquiring HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Needlestick from HIV-infected patient68</td>
<td>0.23% (95% CI 0–0.46%)</td>
</tr>
<tr>
<td>Needlestick injury from discarded needle or syringe from IV drug user69</td>
<td>No cases of transmission reported</td>
</tr>
<tr>
<td>Sexual: unprotected anal89</td>
<td>0.5–3.2%</td>
</tr>
<tr>
<td>Sexual: receptive vaginal89</td>
<td>0.05–0.15%</td>
</tr>
<tr>
<td>Sexual: insertive vaginal89</td>
<td>0.03–0.09%</td>
</tr>
<tr>
<td>Breast milk89</td>
<td>0.001–0.004%</td>
</tr>
</tbody>
</table>

General principles of post-exposure prophylaxis against HIV

The decision on whether or not to recommend post-exposure prophylaxis will depend on factors such as risk and probable adherence. In the absence of data on efficacy outside of the health-care setting, the decision is best made by experienced clinicians in collaboration with the exposed person and/or parents after a careful discussion of the risks of transmission and the burden and potential complications of antiretroviral therapy.91

Some authorities recommend using three drugs for high-risk exposures and fewer for exposures defined as low risk.94 Others recommend consideration of a two-drug regimen (AZT+3-TC) if it is likely to improve compliance. If it is decided to start prophylaxis, it is recommended to start as soon as possible and continue for 4 weeks.91,94 Prophylaxis is not usually
recommended >72 hours after exposure, unless the risk is very high.91,94

Children exposed to HIV may also have been exposed to other blood-borne viruses such as HBV and HCV, in which case they should have prophylaxis against HBV infection (see p. 93) and counseling about risk and follow-up.

If the source is found to be HIV antibody negative, and unlikely to be in the window period between infection and seroconversion, no further follow-up testing is required for the source or child. In all other circumstances, the child should have follow-up HIV antibody testing, usually at 6 weeks, 3 months, and 6 months, together with tests for other blood-borne viruses such as HBV and HCV as indicated.91,94

Post-exposure prophylaxis regimen
If it is decided to give post-exposure prophylaxis, we recommend:

- lamivudine 4 mg/kg (max 150 mg) AND
- zidovudine 8 mg/kg (max 300 mg) orally,
- 12-hourly for 4 weeks or until source shown to be HIV negative PLUS EITHER
- lopinavir 300 mg/m² (max 400 mg) AND
- ritonavir 75 mg/m² (max 100 mg) orally,
- 12-hourly (Kalera) for 4 weeks or until source shown to be HIV negative OR
- nelfinavir <13 years: 55 mg/kg (max 2 g) orally, 12-hourly; >12 years: 1250 mg orally, 12-hourly for 4 weeks or until source shown to be HIV negative

Needlestick exposure to HIV (percutaneous injury)
Needlestick exposure to HIV occurs most commonly from health-care exposure or from discarded IV drug-using equipment. The risks are extremely different.

Exposure to needlestick in health-care setting
A systematic review found 22 studies of needlestick exposure where the source was known to be HIV-infected.88 The mean risk from contaminated needlestick injury was 0.23% (95% CI 0–0.46%) or 1 in 435 needlestick injuries,88 although the estimates ranged from 0 to 2.38%.

Exposure to needlestick in community
Needlestick injuries in the community usually occur when a child handles or steps on a needle and syringe in the park or on a beach. The risk is almost certainly far lower than with health-care exposures, but has not been quantified.

HIV is very susceptible to drying. In the laboratory setting, HIV can survive for up to 28 days in syringes containing as little as 20 μL of blood.95 On the other hand, when HIV is placed on a surface exposed to air, the 50% tissue culture infective dose decreases by about 6 logs in 72 hours (1 log every 9 h).96

No HIV proviral DNA could be detected in 28 syringes discarded in public places and 10 syringes from a needle exchange program for injection drug users.97 We found that over 300 children have been followed up after community needlestick exposures from discarded needles and syringes and none have acquired HIV infection.98–101 We calculated that the 95% CI for the transmission rate is 0–1%. There have been no confirmed reports of HIV acquisition from percutaneous injury by a needle found in the community.89

Parents are understandably upset after an accidental needlestick exposure, and reassurance about the low risk is paramount. We counsel against post-exposure prophylaxis with antiretrovirals in this setting, although we would be guided by the parents if they wanted prophylaxis despite the low risk. We advise to make sure always that the child is protected against hepatitis B virus infection (see p. 93).

Sexual exposure to HIV
The risks of HIV infection from sexual exposure have been explored in a number of studies102–107 and are given in Table 8.4. The risk varies according to the nature of the sexual act. HIV infection has been described following oral sex,108 but the risk from a single episode is unknown and presumably very low. Decisions about whether or not to initiate post-exposure prophylaxis after sexual abuse or rape will need to take into account the risk of HIV infection (see Table 8.4), the potential harms of antiretroviral therapy, and the likelihood of adherence.89

Accidental ingestion of breast milk
It is not uncommon that a baby is accidentally given breast milk expressed by another mother. The risk is extremely low, even if the breast milk is from an
HIV-infected woman89 (see Table 8.4). There are no reports of HIV transmission to a person handling human milk in a nursery from a single episode of exposure to HIV-infected human milk, or to an infant from a single enteral exposure to HIV-infected human milk.89

We do not recommend antiretroviral prophylaxis for accidental ingestion of breast milk, but the risks and benefits of antiretrovirals should be considered and discussed with the baby’s parents.

8.10 Useful Web sites on HIV infection

British HIV Association (BHIVA) Web site includes guidelines on the management of HIV infection: http://www.bhiva.org/


References


21 Kovacs A, Xu J, Rasheed S et al. Comparison of a rapid non-isotopic polymerase chain reaction assay with four commonly used methods for the early diagnosis of human


59 Rueda S, Park-Wyllie LY, Bayoumi AM et al. Patient support and education for promoting adherence to highly active antiretroviral therapy for HIV/AIDS. *The Cochrane Database of Systematic Reviews* 2006; (3):Art No CD001442.


78 Read JS, Newell ML. Efficacy and safety of cesarean delivery for prevention of mother-to-child transmission of HIV-1.


9.1 Febrile neutropenia

Definition of febrile neutropenia

A working definition of febrile neutropenia is fever, defined as a single oral temperature of $\geq 38.3^\circ C$ ($101^\circ F$) or a temperature of $\geq 38.0^\circ C$ ($100.4^\circ F$) for $\geq 1$ hour, together with neutropenia, defined as neutrophils $<500$ cells/mm$^3$ ($0.5 \times 10^9$ cells/L), or $<1000$ cells/mm$^3$ ($1 \times 10^9$ cells/L) with a predicted decline to $<500$ cells/mm$^3$ ($0.5 \times 10^9$ cells/L). In patients with febrile neutropenia, the risk of overwhelming septicemia is sufficiently high, at 20–30%,$^1$−$^3$ that urgent empiric IV therapy with broad-spectrum antimicrobials is a universally accepted principle.$^1$−$^3$

Clinical features in children

A meta-analysis comparing 759 children and 2321 adults with febrile neutropenia enrolled in treatment trials looked at differences in presentation and outcome.$^2$ Children were more likely than adults to have acute lymphoblastic leukemia (ALL) or solid tumors undergoing intensive myelosuppressive therapy, but were less likely to have acute myeloid leukemia (AML). Children were less likely to have a defined site of infection, and had more upper respiratory tract infections but fewer lung infections than adults. There was a similar low incidence of shock at presentation in the two groups but the children’s median neutrophil count was lower, and their median duration of granulocytopenia before the trial was shorter. The incidence of bacteremia was similar, but clinically documented infection was less frequent and fever of unknown origin more common in children.$^2$

In general, the prognosis is better for children. In the review, the mortality from infection was only 1% in children compared with 4% in adults ($p = 0.001$), and time to defervescence was shorter in children.$^2$ In the younger age group, high temperature, prolonged neutropenia before the trial, and shock were prognostic indicators for bacteremia. Solid tumor patients were significantly less likely to have bacteremia.$^2$

Organisms causing febrile neutropenia in children

There has been a well-documented shift since the 1980s, when Gram-negative bacilli were the major cause of bacteremia in adult febrile neutropenic patients, to a predominance of Gram-positive organisms.$^3$ In a meta-analysis, published in 1997, children developed more streptococcal bacteremias and fewer staphylococcal bacteremias than adults ($p = 0.003$) but the relative incidence of Gram-negative bacillary infections was similar.$^2$ We found seven studies published from 2001 to 2005 that reported bloodstream isolates.$^4$−$^{10}$ Overall, Gram-positive cocci were isolated from 65% of episodes; half of these episodes were due to staphylococci, with coagulase negative staphylococci more frequently reported than Staphylococcus aureus, and half were due to streptococci, mostly of the viridans group. Gram-negative bacilli were grown in 22% of episodes and fungi in 5%. Bacteremia due to Pseudomonas aeruginosa is relatively rare, but because mortality is high, empiric regimens usually cover this organism. These data are very similar to the data on adult patients in the USA with nosocomial bloodstream infections associated with neutropenia.$^{11}$

The responsible organisms depend on the degree of immunosuppression, the likelihood of infection, and contamination of indwelling intravascular catheters. The organisms grown and the outcome of infections determine what empiric antimicrobial therapy we should consider. Local data on organisms and their sensitivities often influence antibiotic choices.

Laboratory markers of infection in children with febrile neutropenia

Studies have shown that serum acute phase reactants, such as C-reactive protein, IL-6, IL-8, and procalcitonin, are sensitive and specific indicators of
infection in febrile neutropenic children. Procalcitonin appears to be the best, with a sensitivity >90% and specificity of 90%, but none of the markers has 100% sensitivity. Because febrile neutropenic children, like neonates, can deteriorate rapidly and unpredictably, and because the risk of bacteremia is as high as 20–30%, it is considered mandatory to treat with empiric antibiotics pending the results of cultures. In this case, measurement of acute phase reactants will not guide decisions about starting therapy.

Empiric antibiotic treatment of febrile neutropenia in children

Question | For children with febrile neutropenia, does combination therapy using a beta-lactam and an aminoglycoside compared with monotherapy with a beta-lactam reduce mortality or treatment failures? Is combination therapy more likely than monotherapy to select for resistant organisms?

Literature review | We found 46 RCTs, only 5 of them in children, a Cochrane systematic review, and a non-Cochrane meta-analysis comparing a beta-lactam plus an aminoglycoside with monotherapy. Most of the data on antibiotics come from studies in adults. The Cochrane review included RCTs comparing any beta-lactam antibiotic monotherapy with any combination of a beta-lactam and an aminoglycoside antibiotic, for the initial, empiric treatment of febrile neutropenic cancer patients. It identified 46 trials (7642 patients) but only 5 trials (431 children) were pediatric.

When all 46 studies were combined, there was no significant difference between monotherapy and combination therapy in all-cause mortality (RR 0.85, 95% CI 0.72–1.02). When we analyzed the pediatric studies alone, there were no conclusive results.

When treatment failure was the outcome, there was no significant difference between studies that compared one beta-lactam with the same beta-lactam plus an aminoglycoside, but a significant advantage to monotherapy for studies comparing different beta-lactams (RR 0.86, 95% CI 0.80–0.93). Bacterial and fungal superinfections developed with similar frequencies in the monotherapy and combination treatment groups. Adverse events were significantly more common in the combination treatment group (RR 0.83, 95% CI 0.72–0.97). These included events associated with significant morbidity, primarily renal toxicity.

The authors conclude that the meta-analysis showed an advantage to broad-spectrum beta-lactam monotherapy over beta-lactam/aminoglycoside combination therapy for febrile neutropenia (in adults). The advantages were (1) a similar, if not better, survival, (2) a significantly lower treatment failure rate, (3) comparable probability for secondary infections, and (4) most importantly, a lower rate of adverse events associated with significant morbidity. They conclude that monotherapy should be regarded as the standard of care for febrile neutropenic patients. While their data are primarily in adults, the pediatric data are not inconsistent with their conclusions. The non-Cochrane review of 29 studies (4795 episodes) found that monotherapy was better than combination therapy in terms of mortality and treatment failures.

A separate meta-analysis of eight RCTs compared the effects of the two different regimens on resistance. Beta-lactam monotherapy was associated with significantly fewer superinfections (OR 0.62, 95% CI 0.42–0.93) and fewer treatment failures (OR 0.62, 95% CI 0.38–1.01) than the aminoglycoside/beta-lactam combination, and there was a trend for monotherapy to be associated with a lower emergence of resistant organisms (OR 0.90, 95% CI 0.56–1.47).

For children with febrile neutropenia, we recommend using monotherapy with a beta-lactam antibiotic with activity against Pseudomonas.

Question | For children with febrile neutropenia, does the addition of an antibiotic with enhanced activity against Gram-positive organisms such as vancomycin or teicoplanin compared with the standard empiric antibiotic regimen reduce mortality or treatment failures?

Literature review | We found 13 RCTs and a Cochrane review comparing the addition of an antibiotic with enhanced Gram-positive activity to a standard regimen. None were in children. We found 2 RCTs in children which compared two different regimens, 1 of which included vancomycin.

A Cochrane review included RCTs where only one antibiotic regimen for the treatment of febrile neutropenic cancer patients was compared to the same regimen with the addition of an antibiotic active...
against Gram-positive organisms (usually vancomycin or teicoplanin). It included 13 trials and 2392 patients. Empiric anti-Gram-positive antibiotics were given at the onset of treatment in 11 studies and for persistent fever in 2 studies. The addition of an antibiotic with Gram-positive activity did not decrease mortality or treatment failures. The authors conclude that the use of vancomycin or teicoplanin as empiric therapy or added later without proof of a Gram-positive infection does not improve outcome. The two studies in children showed that regimens that included vancomycin conferred no added advantage over standard regimens without vancomycin.

We do not recommend empiric use of vancomycin or teicoplanin for children with febrile neutropenia.

Question | For children with febrile neutropenia, does one regimen compared with other regimens reduce mortality or treatment failures or antibiotic resistance?

Literature review | We found 33 RCTs and a non-Cochrane systematic review comparing different beta-lactams used with or without vancomycin. Five of these studies were in children. We found 8 RCTs and a non-Cochrane meta-analysis comparing ceftriaxone with an antipseudomonal beta-lactam.

Monotherapy using a beta-lactam antibiotic with activity against *Pseudomonas* is an accepted regimen for febrile neutropenia, and is supported by the evidence. Although a meta-analysis of eight trials found no difference between ceftriaxone, an antibiotic with no useful antipseudomonal activity, and beta-lactam antibiotics with activity against *Pseudomonas*, the studies were done at a time when *Pseudomonas* infection was very uncommon and most authorities would not recommend ceftriaxone monotherapy for febrile neutropenia.

A non-Cochrane systematic review and meta-analysis of RCTs compared different antipseudomonal beta-lactams, given with or without vancomycin. Thirty-three trials fulfilled inclusion criteria, of which five were in children. Cefepime was associated with higher all-cause mortality at 30 days than other beta-lactams (RR 1.44, 95% CI 1.06–1.94, 3123 participants). Carbapenems (imipenem or meropenem) were associated with fewer treatment modifications, including addition of glycopeptides, than ceftazidime or other comparators. Adverse events were significantly more frequent with carbapenems, specifically pseudomembranous colitis (RR 1.94, 95% CI 1.24–3.04). All-cause mortality was unaltered. Piperacillin/tazobactam was compared only with ceftepime and carbapenems in six trials. No significant differences were demonstrated, but there was insufficient data to be certain about all-cause mortality.

The increased mortality associated with ceftepime is unexplained. For the three pediatric studies (263 children) there was a trend toward higher mortality with ceftepime when compared with ceftazidime (RR 2.28, 95% CI 0.53–9.79) and no difference in the one study that compared ceftepime with meropenem. Empiric use of carbapenems was associated with an increased rate of pseudomembranous colitis. The use of quinolones, such as ciprofloxacin, although effective either as monotherapy or in combination, is discouraged because of the rapid emergence of resistance.

Ceftazidime, piperacillin/tazobactam, imipenem/cilastatin, and meropenem appear to be suitable agents for monotherapy. We prefer to keep carbapenems in reserve for multiresistant organisms.

For the empiric treatment of children with fever and neutropenia, unless there are local factors such as organisms resistant to these antibiotics, we recommend:

- ceftazidime 50 mg/kg (max 2 g) IV, 8-hourly
- piperacillin/tazobactam 100 + 12.5 mg/kg (max 4 + 0.5 g) IV, 8-hourly

Question | For children with cancer or other causes of severe immune compromise being treated with aminoglycosides, is once-daily compared with multiple-daily dosing safe and effective?

Literature review | We found six RCTs in febrile neutropenic children comparing once-daily with multiple-daily dosing of aminoglycosides. Studies in febrile neutropenic children have shown that once-daily aminoglycoside treatment is less nephrotoxic and at least as effective as multiple-daily dosing. All but one of the studies, however, included other antibiotics such as beta-lactams, which made interpretation of the data uncertain. As a result, once-daily therapy has not yet been recommended routinely when using aminoglycosides to treat children with fever and neutropenia. Subsequent to the 2002
US guidelines,1 a study of tobramycin monotherapy in febrile neutropenic children undergoing stem cell transplantation found once-daily tobramycin was less nephrotoxic and more efficacious than thrice daily.38 The evidence appears to be accumulating that once-daily dosing of aminoglycosides is safer than multiple-daily dosing and at least as effective. Because immune compromised children vary in their degree of immune compromise and their renal function, studies may be needed in a number of different settings.

We believe the evidence favors once-daily dosing of aminoglycosides for the majority of children with cancer or immune compromise.

Outpatient management of febrile neutropenia

It is possible to identify a group of febrile neutropenic children at low risk for bacteremia, who might be considered for outpatient management. In an observational study,39 children were defined as low risk if they were outpatients at the time of presentation with febrile neutropenia, had an anticipated duration of neutropenia <7 days, and no significant comorbidity. They were compared with febrile neutropenic children not meeting the low-risk criteria, who were defined as high risk. The low-risk children had fewer episodes of bacteremia, other documented infection, and serious medical complications compared to the high-risk group, and shorter duration of neutropenia and hospital stay, but no shorter duration of fever. Overall, the rate of any adverse event was 4% in the low-risk group compared with 41% in the high-risk group. Thus, it is possible to identify a low-risk group, using simple readily available criteria. There are obvious dangers in trying to manage even low-risk children with febrile neutropenia as outpatients, but an economic analysis favored the use of home-based care for low-risk children.40

If no organism is grown, the child becomes afebrile and remains afebrile, and the neutrophil count recovers to >500 cells/mm³ (500 × 10⁹ cells/L) in less than 7 days, a number of studies have shown that antibiotics can be stopped safely.41–44 However, the IDSA guidelines recommend continuing with oral cefixime to a total of 7 days, citing a lack of good evidence for stopping earlier.1

If an organism is grown, therapy should be changed to the most appropriate regimen to treat that organism. The optimum duration of therapy for proven infection is unknown, but the IDSA recommends at least 7 days.1

Persistent fever and neutropenia

If fever and neutropenia persist, but cultures are negative, there are a number of options.

Question | For a child with febrile neutropenia that persists after 3–5 days with negative blood cultures, does stopping antibiotics compared with continuing the same empiric antibiotics compared with adding vancomycin or teicoplanin compared with adding one or more antifungals decrease morbidity or increase treatment failures or mortality?

Literature review | We found 1 RCT comparing stopping antibiotics with continuing antibiotics and with adding amphotericin.45 We found 2 studies comparing adding vancomycin or teicoplanin with continuing antibiotics.46,47 We found 31 studies and a Cochrane review of antifungals.

Continuing antibiotic treatment for prolonged fever and neutropenia

In an early study, 50 child, adolescent, and adult patients with persistent fever and neutropenia despite 7 days of antibiotics (cephalothin, gentamicin, and carbenicillin) were randomized to discontinue antibiotics (Group 1), to continue antibiotics (Group 2), or to continue antibiotics and add empiric amphotericin B (Group 3).45 The duration of neutropenia was comparable in the three groups (median 24 days, range 8–51 days). Clinically or microbiologically demonstrable infections occurred in 9 of 16 patients who discontinued antibiotics (Group 1) (6 also experienced shock, p < 0.01), in 6 of 16 who continued antibiotics (Group 2) (fungal infection developed in 5), and in 2 of 18 who continued antibiotics plus amphotericin B (Group 3).
The incidence of infections was lower for patients receiving antibiotics plus amphotericin B (Group 3) than for patients in Group 1 who discontinued antibiotics ($p = 0.013$). There has only been one RCT exclusively in children of stopping antibiotics despite persistent fever and neutropenia. In this study from Chile, about a third of all children with febrile neutropenia could be defined on admission as low risk for bacterial infection and had negative blood cultures on day 3. The 68 low-risk children (75 episodes) were randomized to continue or to stop antibiotics. There were few infections and no deaths.

Because patients with persistent fever and neutropenia have a high rate of subsequent infection with bacteria or fungi and because of the high mortality from such infections, it is not recommended to stop all antimicrobial therapy and observe children with persistent fever and neutropenia.

The use of antifungals for persistent fever in febrile neutropenia was examined in a Cochrane review. The review included 31 RCTs of different antifungals compared with placebo or no treatment in 4155 cancer patients with neutropenia. Unfortunately, the review combines studies of antifungal prophylaxis with studies of antifungals given empirically for persistent fever. The incidence of invasive fungal infection decreased significantly with administration of amphotericin B (RR 0.39, 95% CI 0.20–0.76), fluconazole (RR 0.39, 95% CI 0.27–0.57), and itraconazole (RR 0.53, 95% CI 0.29–0.97), but not with miconazole or ketoconazole.

Prophylactic or empiric treatment with antifungals as a group had no statistically significant effect on mortality (RR 0.96, 95% CI 0.83–1.11). Amphotericin B showed a trend toward reduced mortality (RR 0.73, 95% CI 0.52–1.03), but fluconazole, ketoconazole, miconazole, and itraconazole did not reduce mortality.

We recommend starting antifungal therapy for children with fever and neutropenia that persists for more than 5 days.

Empiric use of antifungals for persistent fever and neutropenia

There are four classes of antifungals used for invasive fungal infections: polyenes (amphotericin B and lipid formulations of amphotericin), azoles (fluconazole, itraconazole, voriconazole, and posaconazole), echinocandins (caspofungin), and nucleoside analogues (flucytosine). The polyenes and azoles target ergosterol in the fungal cell membrane, echinocandins interfere with cell wall biosynthesis, and nucleoside analogues interfere with nucleotide synthesis.

**Question** For children with persistent fever and neutropenia, is one antifungal regimen compared with other regimens safe and effective and cost-effective?

**Literature review** We found 1 RCT and a Cochrane review comparing liposomal amphotericin with voriconazole. We found 4 RCTs and a Cochrane review comparing fluconazole with conventional amphotericin B. We found 1 RCT comparing itraconazole with conventional amphotericin B. We found 1 RCT comparing liposomal amphotericin with caspofungin. We found 12 RCTs and a Cochrane review comparing lipid soluble formulations of amphotericin B with conventional amphotericin B.

**Liposomal amphotericin versus voriconazole for persistent fever and neutropenia**

We found one RCT comparing liposomal amphotericin with voriconazole in 849 patients > 12 years old with fever > 96 hours. The trial was sponsored by the pharmaceutical company marketing voriconazole. The study authors claimed no difference in mortality, but a significant reduction in the number of breakthrough fungal infections with voriconazole. The study was considered in a Cochrane review. The Cochrane reviewers felt voriconazole was significantly inferior to liposomal amphotericin B according to the authors’ prespecified criteria. More patients died in the voriconazole group (RR 1.37, 95% CI 0.96–1.96, $p = 0.10$), and the claimed significant reduction in the number of breakthrough fungal infections disappeared when patients arbitrarily excluded from analysis by the authors were included.

**Fluconazole versus conventional amphotericin B for persistent fever and neutropenia**

We found four RCTs, none of them in children, and a Cochrane review comparing fluconazole with conventional amphotericin B for fluconazole-naive cancer patients with persistent fever and neutropenia. Fluconazole was at least as effective as conventional amphotericin B and less toxic.
**Itraconazole versus conventional amphotericin B for persistent fever and neutropenia**

A single RCT found that itraconazole (IV, then oral) was equivalent to conventional amphotericin B in efficacy and less toxic in patients with persistent fever and neutropenia.56

**Liposomal amphotericin versus caspofungin for persistent fever and neutropenia**

A large RCT found that caspofungin had comparable efficacy to liposomal amphotericin, and was associated with less nephrotoxicity and fewer infusion-related events.57 At present, the price of caspofungin exceeds that of all other antifungals considerably. We do not recommend its use unless it is shown to be cost-effective compared with other antifungals.

**Liposomal amphotericin versus conventional amphotericin B for persistent fever and neutropenia**

A Cochrane review58 found 12 RCTs comparing lipid-soluble formulations of amphotericin B with conventional amphotericin B for the treatment or prophylaxis of neutropenic cancer patients. Only two studies were in children. Lipid-based amphotericin B was not more effective than conventional amphotericin B for mortality (RR 0.83, 95% CI 0.62–1.12), but decreased invasive fungal infection (RR 0.65, 95% CI 0.44–0.97), nephrotoxicity, defined as a 100% increase in serum creatinine (RR 0.45, 95% CI 0.37–0.54), and number of treatment dropouts (RR 0.78, 95% CI 0.62–0.97).

For liposomal amphotericin (AmBisome), the drug used in most patients, a meta-analysis of three trials (1149 patients) found no significant difference in mortality (RR 0.74, 95% CI 0.52–1.07) whereas it tended to be more effective than conventional amphotericin B for invasive fungal infection (RR 0.63, 95% CI 0.39–1.01, p = 0.053).58

AmBisome, amphotericin B in Intralipid (six trials, 379 patients), amphotericin B colloidal dispersion (ABCD) (two trials, 262 patients), and amphotericin B lipid complex (ABLC) (one trial, 105 patients) all decreased the occurrence of nephrotoxicity, but conventional amphotericin B was rarely administered under optimal circumstances.58

A pharmacoeconomic analysis compared the additional cost of liposomal amphotericin against the costs of toxicity from conventional amphotericin B for adult patients.59 The analysis favored conventional amphotericin B, but was very sensitive to the cost of the drugs. Because of the risk of cumulative nephrotoxicity, most authorities prefer liposomal amphotericin to conventional amphotericin B, provided it can be afforded and its use does not divert funds from other more effective treatments.

**Continuous infusion of conventional amphotericin B for persistent fever and neutropenia**

An RCT of 80 mostly neutropenic patients with refractory fever and suspected or proved invasive fungal infections compared 1 mg/kg conventional amphotericin B given either by continuous infusion over 24 hours or by rapid infusion over 4 hours.60 Patients in the continuous infusion group had fewer side effects and significantly reduced nephrotoxicity than those in the rapid infusion group. The overall mortality was significantly lower during treatment and after 3 months’ follow-up in the continuous infusion group.60

The study was small and did not include bone marrow transplant patients or patients on cyclosporine, so the results should not be generalized without further studies. Despite the success of this study, there have been no further RCTs comparing continuous infusion of conventional amphotericin B with the newer, far more expensive drugs, such as liposomal amphotericin, voriconazole, and caspofungin. It is difficult not to be cynical about the reason for the dearth of studies. Such studies would be extremely welcome.

**Recommended empiric antifungal therapy for prolonged fever and neutropenia**

We define patients at high risk of nephrotoxicity as:

- hematopoietic stem cell recipients;
- children with underlying renal insufficiency;
- children receiving two or more nephrotoxic drugs;
- children who develop nephrotoxicity on conventional amphotericin B.

The rest are low risk. For patients at low risk of nephrotoxicity who have prolonged fever with neutropenia >5 days, we recommend:

- **amphotericin 1 mg/kg IV, daily OR** (if fluconazole-naïve)
- **fluconazole 6 mg/kg IV, daily (not if Aspergillus infection likely)**
The risk of nephrotoxicity with conventional amphotericin B can be reduced by prior hydration and of infusion-related adverse events by premedication with corticosteroids or acetaminophen.\textsuperscript{50} We recommend changing patients to liposomal amphotericin if they develop nephrotoxicity while taking conventional amphotericin, defined as a doubling or rapid rise in serum creatinine.\textsuperscript{50}

For high-risk patients who have prolonged fever with neutropenia $>5$ days, we recommend:

**liposomal amphotericin** 1 mg/kg IV, daily **OR**

*voriconazole* 6 mg/kg IV, 12-hourly for two doses, then 4 mg/kg IV, 12-hourly

Although it is tempting to recommend continuous infusion of amphotericin, the data are not yet sufficiently robust.

**Recommended antifungal therapy for candidemia or invasive candidosis**

In non-neutropenic patients, a non-Cochrane meta-analysis found that fluconazole was as effective as conventional amphotericin B and less toxic.\textsuperscript{61} No other RCTs have shown that any other antifungal is superior to fluconazole or conventional amphotericin B for invasive candidiasis, although caspofungin was shown to be at least as effective as conventional amphotericin B.\textsuperscript{62} Prior fluconazole therapy is a risk factor for fluconazole-resistant candidiasis,\textsuperscript{63} so amphotericin B is preferred for children who have previously received fluconazole.

For fluconazole-naïve children, we recommend:

**fluconazole** 6 mg/kg IV, daily

For children with fluconazole-resistant *Candida* and children who have already received fluconazole, if they are at low risk for renal impairment, we recommend:

**amphotericin** 1 mg/kg IV, daily

For children with fluconazole-resistant *Candida* and children who have already received fluconazole who have preexisting renal impairment or are at high risk of developing it, we recommend:

**liposomal amphotericin** 3 mg/kg IV, daily **OR**

*voriconazole* 6 mg/kg IV, 12-hourly for two doses, then 4 mg/kg IV, 12-hourly

**Recommended antifungal therapy for invasive aspergillosis**

An RCT compared voriconazole with conventional amphotericin B for confirmed and presumed invasive *Aspergillus* infections in 391 patients 12 years or older with mainly hematologic malignancies or stem cell transplants.\textsuperscript{64} The trial was sponsored by the pharmaceutical company marketing voriconazole. The study authors reported that voriconazole had significant benefit at 12 weeks, in terms of response to therapy and mortality.\textsuperscript{64} A Cochrane review commented, however, that conventional amphotericin B was used without adequate attention to reducing its adverse effects by premedication and hydration.\textsuperscript{50} This resulted in a marked difference in the duration of treatment on trial drugs (77 days with voriconazole versus 10 days with amphotericin B), and they felt precluded meaningful comparisons of the benefits and harms of the two drugs.\textsuperscript{50}

Liposomal preparations of amphotericin are less toxic but have not been shown to be more effective than conventional amphotericin B for invasive aspergillosis. An RCT found that ABCD was almost identical to conventional amphotericin B in terms of response and mortality, was less nephrotoxic, but costs far more.\textsuperscript{65} We recommend:

*voriconazole* 6 mg/kg IV 12-hourly for two doses, then 4 mg/kg IV 12-hourly for at least 7 days, then 4 mg/kg (max 200 mg) orally 12-hourly **OR**

**liposomal amphotericin** 3–5 mg/kg IV, daily **OR**

amphotericin B desoxycholate 1 mg/kg IV, daily

[*It is recommended that voriconazole levels be monitored.]*

**Empiric use of glycopeptide antibiotic for persistent fever and neutropenia**

Two RCTs compared the addition of glycopeptides, vancomycin,\textsuperscript{43} or teicoplanin,\textsuperscript{44} with continuing therapy in patients with fever that persisted for 72–96 hours. They found no benefit, and concluded that a glycopeptide such as vancomycin should not be started empirically unless there is evidence of infection with a vancomycin-susceptible organism, such
as MRSA. A Cochrane review came to the same conclusion.\textsuperscript{22}

We do not recommend adding vancomycin or teicoplanin for persistent fever and neutropenia routinely, unless positive blood cultures are positive for a sensitive organism.

Preventive therapy for children with febrile neutropenia

Prophylactic antibiotics in febrile neutropenic patients

\textbf{Question} | For neutropenic children who are afebrile but at risk of bacterial infection, do prophylactic antibiotics compared with no antibiotics or placebo reduce the incidence of bacterial infection and do they increase antibiotic resistance?

\textbf{Literature review} | We found 101 trials and a Cochrane review.\textsuperscript{66}

A Cochrane review of RCTs or quasi-RCTs compared different types of antibiotic prophylaxis with placebo or no intervention or another antibiotic to prevent bacterial infections in febrile neutropenic patients.\textsuperscript{66} They included 101 trials (12,599 patients) performed between the years 1973 and 2005. Antibiotic prophylaxis significantly decreased the risk for death when compared with placebo or no intervention (RR 0.66, 95\% CI 0.55–0.79). The authors estimated that 50 patients needed to be treated to prevent one death from all causes. Prophylaxis resulted in a significant decrease in the risk of infection-related death (RR 0.59, 95\% CI 0.47–0.75) and in the occurrence of fever (RR 0.77, 95\% CI 0.74–0.81). A reduction in mortality was also evident when the more recently conducted quinolone trials were analyzed separately. Quinolone prophylaxis reduced the risk for all-cause mortality (RR 0.52, 95\% CI 0.37–0.74).

Although the authors recommend that antibiotic prophylaxis should be considered, particularly with a quinolone,\textsuperscript{66} current recommendations do not favor prophylaxis, because of the risk of resistance.\textsuperscript{1,2}

We do not recommend prophylactic antibiotics to prevent bacterial infections in afebrile neutropenic patients, except trimethoprim-sulfamethoxazole to prevent PCP (see Section 9.4, p. 126).

Prophylactic antifungals in febrile neutropenia

\textbf{Question} | For neutropenic children who are afebrile but at risk of fungal infection, do prophylactic antifungals compared with no antifungals or placebo reduce the incidence of fungal infection and do they increase antifungal resistance?

\textbf{Literature review} | We found 31 RCTs and a Cochrane review of prophylactic antifungals for neutropenic patients.\textsuperscript{48} We found 12 RCTs and a Cochrane review of antifungal prophylaxis in non-neutropenic, critically ill adult patients.\textsuperscript{67}

As previously stated (see p. 121), a Cochrane review of randomized trials of antifungals in cancer patients with neutropenia did not separate prophylaxis from treatment.\textsuperscript{48} This review found that antifungals reduced the incidence of fungal infections but not the mortality.

A Cochrane review of antifungal prophylaxis in non-neutropenic, critically ill adult patients found 12 trials (8 fluconazole and 4 ketoconazole) involving 1606 randomized patients.\textsuperscript{67} When combined, fluconazole or ketoconazole reduced total mortality by about 25\% (RR 0.76, 95\% CI 0.59–0.97) and invasive fungal infections by about 50\% (RR 0.46, 95\% CI 0.31–0.68). Prophylactic antifungals were not associated with a detectable increase in the incidence of infection or colonization with theazole-resistant fungal pathogens Candida glabrata or C. krusei, although the confidence intervals were wide and trials were not powered to exclude such an effect. Adverse effects were not more common among patients receiving prophylaxis.

We recommend that antifungal prophylaxis with fluconazole should be considered for patients at increased risk of invasive fungal infections.

Colony-stimulating factors to prevent febrile neutropenia

A Cochrane review found six studies (332 participants) of the use of colony-stimulating factors to prevent febrile neutropenia in children with ALL.\textsuperscript{68} The use of colony stimulating factors significantly reduced the number of episodes of febrile neutropenia, the length of hospitalization, and the number of infectious disease episodes, but did not influence the length of episodes of neutropenia. There were insufficient data to assess the effect on survival. There was substantial heterogeneity.
Immune deficiency between included trials. The role of cerebrospinal fluid for preventing febrile neutropenia episodes is still uncertain.

9.2 Immunization and leukemia

Children with acute leukemia and other malignancies who have been previously immunized often lose antibodies to vaccine antigens. It is not clear whether this means they have become susceptible to those diseases and so whether or not they need booster doses of vaccine. When the vaccines are live vaccines such as measles or VZV vaccines that are contraindicated for immunodeficient children, it is not clear whether or not the children need passive protection if they are exposed to wild-type disease.

A non-Cochrane systematic review found eight studies published since 1980 on vaccination of children with ALL. The number of children who had preserved defined protective titers of antibodies after treatment for ALL ranged from 17 to 98% for diphtheria, from 27 to 82% for Bordetella pertussis, from 20 to 98% for tetanus, from 62 to 100% for poliomyelitis, from 35 to 100% for Haemophilus influenzae type b (Hib), from 29 to 92% for mumps, from 29 to 60% for measles, and from 72 to 92% for rubella. Most patients, however, responded to revaccination, demonstrating immunological recovery. Although the designs and results of the included studies varied widely, it can be concluded that chemotherapy for ALL in children results in a temporary reduction of specific antibody levels. Memory is preserved but revaccination may be warranted.

9.3 Prevention of sepsis due to asplenia or splenectomy

Children with functional or anatomic asplenia are at increased risk from infections with encapsulated organisms, particularly pneumococci. Asplenic patients present with high fever and rapidly develop shock or purpura fulminans. In a paper reporting 26 episodes of pneumococcal sepsis in 22 asplenic patients, 7 had shock, 7 had petechiae or purpura, 5 had disseminated intravascular coagulation, and 5 had respiratory distress Six died (27%).

Guidelines on the management of children with functional or anatomical asplenia have been published. The most common problem concerning asplenia in children is functional asplenia due to sickle cell disease. Before the use of penicillin prophylaxis, pneumococcal polysaccharide vaccines, and neonatal screening for hemoglobinopathies, rates of invasive pneumococcal disease in children with sickle cell disease were 20- to 100-fold higher than those in healthy children, with the greatest risk in children <5 years old. Children with sickle cell hemoglobinopathy and certain other sickle cell hemoglobinopathies (including thalassemias) have lower rates of infection than children with SS hemoglobinopathy, but their rates are much higher than those of other children, and deaths attributable to fulminant pneumococcal infection have been reported in these children as well. Despite the use of pneumococcal polysaccharide vaccines and penicillin prophylaxis, high rates of invasive pneumococcal infection have continued to be observed in some groups of children with sickle cell disease.

The risk of post-splenectomy sepsis was examined in a non-Cochrane meta-analysis of 19,680 adults and children followed for a mean of 6.9 years. The incidence of infection was 3.3% for children and 3.2% for adults, and the mortality was 1.7% for children and 1.3% for adults. The incidence of sepsis was even higher in 200 children splenectomized as part of their staging for Hodgkin lymphoma: there were 20 episodes in 18 children, and 8 died (4% overall mortality). The risk of sepsis in children with congenital asplenia, usually associated with congenital heart disease, is extremely high. In a review, 59 children with congenital asplenia (7 with isolated asplenia and 52 with complex congenital heart disease) were compared with a control group of eusplenic children with comparable cardiac lesions. Sixteen (27%) of the asplenic children had documented sepsis. In children <6 months of age, the organism was usually a Gram-negative bacillus (Escherichia coli or Klebsiella), but from 6 months on was usually Streptococcus pneumoniae or H. influenzae. Children with asplenia syndrome who survived the first month of life were at greater risk of dying from sepsis than from their heart disease. The data support giving prophylactic antibiotics to children with congenital asplenia. For children with congenital asplenia, consideration should be given to using amoxicillin-clavulanic acid or ciprofloxacin in the first 6 months because of the risk of Gram-negative sepsis and to switching to amoxicillin at 6 months.
Antibiotic prophylaxis for patients with anatomical or functional asplenia

Antibiotic prophylaxis is recommended for all children with sickle cell disease beginning at 2 months of age or earlier, as well as children with congenital asplenia or surgical splenectomy.70–74 These recommendations are based on demonstrated efficacy against invasive pneumococcal infection in children with sickle cell disease.82,83 In a prospective multicenter, double-blind RCT of prophylactic penicillin administration (125 mg of penicillin V potassium, administered orally twice daily to 3 years of age, and 250 mg twice daily thereafter), the antibiotic prophylaxis group had an 84% decrease in the incidence of pneumococcal infection.82 In another prospective RCT, infants given monthly IM benzathine penicillin injections at home were compared with infants receiving a 14-valent pneumococcal polysaccharide vaccine.83 No episodes of pneumococcal infection occurred among the infants with sickle cell disease receiving benzathine penicillin compared with 10 cases in concurrently followed infants who were immunized but not given monthly injections of penicillin.83

A multicenter RCT of children with sickle cell disease examined the safety of stopping penicillin prophylaxis after 5 years of age.84 Children with sickle cell disease or thalassemia who had received at least 2 years of penicillin prophylaxis and one dose of pneumococcal polysaccharide vaccine before their fifth birthday were randomized to receive continued prophylaxis or placebo. There was no difference in the rate of invasive pneumococcal infection among the children receiving penicillin prophylaxis, four cases (2%), and those receiving placebo, two cases (1%).84

Pneumococcal immunization does not prevent all cases of pneumococcal sepsis.77,78 It used to be thought that the risk from post-splenectomy sepsis was mostly within the first few years, but in one large series, most cases of post-splenectomy sepsis occurred after 10–30 years and only 11% within 4 years of splenectomy.85 In contrast, a retrospective study of 318 patients aged 10–26 years and followed for up to 17 years found that overwhelming post-splenectomy infection (OPSI) occurred in 18 patients (5.7%), 56% within the first 6 months.79 The rate in patients on regular and irregular prophylactic oral penicillin was 2.7% and 10%, respectively (p < 0.01). The incidence of OPSI also decreased from 7.3 to 3.2% after routine administration of pneumococcal vaccine (p < 0.05).86 Antibiotic prophylaxis may be beneficial after 5 years of age, but there are scanty data to support it.

Currently the USA72 and Canada73 recommend stopping antibiotic prophylaxis at 5 years or 1 year after splenectomy,72 provided the child is immunized against pneumococcus, whereas the British recommend that lifelong prophylactic antibiotics should be offered in all cases of asplenia, especially in the first 2 years after splenectomy, for all up to age 16 and when there is underlying impaired immune function.74

Immunizations for patients with anatomical or functional asplenia

Patients with anatomic or functional asplenia can safely be given both live attenuated and killed vaccines.72–74 As these patients are at high risk for developing life-threatening infection due to all encapsulated bacteria, additional immunizations against S. pneumoniae, H. influenzae type b, and Neisseria meningitidis are recommended.72–74,87,88

In patients having elective splenectomy, it is recommended to complete immunizations at least 2 weeks prior to the date of surgery because this improves the immune response.72–74

In case of emergency splenectomy, the patient should be immunized post-splenectomy. Acceptable antibody levels have been demonstrated after vaccination with 23-valent polysaccharide pneumococcal vaccine when the vaccine was given as early as the first day postoperatively.89 However, patients receiving the vaccination within 14 days post-operatively are more likely to require revaccination and the antibody levels achieved in adult, post-splenectomy patients, although protective, are lower than the levels attained by healthy adult subjects.90 It is recommended to immunize patients undergoing emergency splenectomy for trauma 14 days or more after surgery.91,92

A summary of our recommendations, based on the evidence in Section 9.3 (p. 125), is given in Table 9.1.

9.4 Prophylaxis against PCP

Trimethoprim-sulfamethoxazole (TMP-SMX; cotrimoxazole) reduces the risk of P. jiroveci (previously P. carinii) pneumonia (still called PCP) in children with impaired T-cell function at increased risk of PCP
Table 9.1 Recommendations to reduce risk of infections in children with anatomical or functional asplenia.72–74,87,88

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Under 24 mo</th>
<th>2–5 yr</th>
<th>Over 5 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic prophylaxis</td>
<td>Penicillin V 125 mg, orally, daily or amoxicillin 10 mg/kg orally, 12-hourly</td>
<td>Penicillin V 125 mg, orally, 12-hourly or amoxicillin 10 mg/kg orally, 12-hourly</td>
<td>Not recommended, but should wear Medi-Alert bracelet and review fevers early in hospital</td>
</tr>
<tr>
<td>Pneumococcal vaccines</td>
<td>Give pneumococcal conjugate vaccine: primary course and booster dose at 12 months plus dose of pneumococcal polysaccharide vaccine at 2 year of age</td>
<td>Two doses of conjugate vaccine 2 months apart, and then single dose of pneumococcal polysaccharide vaccine at least 1 month later (if not previously immunized)</td>
<td>Two doses of conjugate vaccine 2 months apart, and then single dose of pneumococcal polysaccharide vaccine at least 1 month later (if not previously immunized)</td>
</tr>
<tr>
<td>Hib conjugate vaccine</td>
<td>As per routine childhood schedule</td>
<td>Single dose</td>
<td>Single dose</td>
</tr>
<tr>
<td>Meningococcal vaccines</td>
<td>Give conjugate vaccine at 2, 4, 6 months. Give single dose if over 1 year of age</td>
<td>Give single dose of conjugate vaccine, and then single dose of polysaccharide vaccine at least 1 month later</td>
<td>Give single dose of conjugate vaccine, then single dose of polysaccharide vaccine at least 1 month later</td>
</tr>
</tbody>
</table>

including cancer patients in developed countries93 and HIV-infected children in developing countries.94,95 It is effective when given thrice weekly.96 Toxicity to TMP-SMX is much less common in children than in adults.97 Alternatives in the event of severe rash or other toxicity to TMP-SMX are dapsone98 and IV or aerosolized pentamidine.99

For children with impaired T-cell function, we recommend:

**trimethoprim+sulfamethoxazole**
(trimethoprim 150 mg/m² + sulfamethoxazole 750 mg/m²) orally, as a single dose, thrice weekly on consecutive days, e.g.,
Monday–Tuesday–Wednesday OR
trimethoprim+sulfamethoxazole 4 + 20 mg/kg (max 80 + 400 mg) orally, as a single dose, thrice weekly on consecutive days, e.g.,
Monday–Tuesday–Wednesday OR
dapsone 2 mg/kg (max 100 mg) orally, daily or 4 mg/kg (max 200 mg), once a week OR
pentamidine 4 mg/kg (max 300 mg) IV or aerosolized every 4 weeks

References


23 Granowetter L, Wells H, Lange BJ. Ceftazidime with or without vancomycin vs. cephalothin, carbencillin and gentamicin as the initial therapy of the febrile neutropenic pediatric cancer patient. *Pediatr Infect Dis J* 1988;7:165–70.


59 Cagnoni PJ, Walsh TJ, Prendergast MM et al. Pharmaecoconomic analysis of liposomal amphotericin B versus conventional amphotericin B in the empirical treatment...
CHAPTER 10
Meningitis and central nervous system infections

10.1 Bacterial meningitis

The organisms causing bacterial meningitis vary according to the age of the child. Neonates and babies in the post-neonatal period (up to about 3 mo old) are susceptible to organisms from the maternal genital tract, including group B streptococcus, *Streptococcus faecalis*, *Escherichia coli*, other Gram-negative bacilli, and *Listeria*.1–4

The main organisms causing bacterial meningitis in the post-neonatal period are organisms acquired through the respiratory route, *S. pneumoniae* (pneumococcus), *Neisseria meningitidis* (meningococcus), *Haemophilus influenzae* type b (Hib), and, in some countries, *Salmonella*.1

Clinical diagnosis of bacterial meningitis

The classical clinical presentation of bacterial meningitis is with fever, headache, and neck stiffness.1 Similar signs are found in viral meningitis, but children with bacterial meningitis are usually sicker than children with viral meningitis. For example, one study of children with meningeal signs found that a shorter presenting illness, vomiting, signs of meningeal irritation, cyanosis, petechiae and disturbed consciousness were independent clinical predictors of bacterial meningitis.5 The only independent predictor from subsequent laboratory tests was the serum C-reactive protein (CRP) concentration.5 In a developing country, clinical predictors of bacterial meningitis were appearing sick, being lethargic or unconscious, poor feeding, stiff neck, and bulging fontanelle.6

While clinical signs can suggest a diagnosis of bacterial as opposed to viral meningitis, lumbar puncture is necessary to make the definitive diagnosis for an individual child, to direct antibiotic and other therapy, and to help advise on prognosis (see below).

Laboratory diagnosis of bacterial meningitis

Lumbar puncture (LP)

Which child should have an LP?
The LP is a form of biopsy. Gram stain and cell count are rapidly available after LP, and may suggest which organism is present, may point to an alternate diagnosis (viral meningitis, tuberculous meningitis, subarachnoid hemorrhage, etc.), or may exclude meningitis altogether. Rapid assays on cerebrospinal fluid (CSF) may reveal the organism causing bacterial meningitis even if culture does not, and a positive CSF culture gives antibiotic susceptibility. These are potent reasons for doing an LP when meningitis is suspected. Yet many young doctors are reluctant to perform LP nowadays.

In some situations, it may be unsafe to perform an immediate LP because of the risk of provoking cerebral herniation (“coning”). The signs of impending cerebral herniation are deterioration in level of consciousness, rising blood pressure, falling heart rate, cranial nerve signs, decorticate or decerebrate posturing.7–10 All children with bacterial meningitis have raised intracranial pressure,7,8 and cerebral herniation can occur without LP. Cerebral herniation is reported to occur in 4–6% of children with bacterial meningitis, with or without LP.8–10 In some children, the onset of signs of cerebral herniation coincided with LP, but it is unclear whether or not LP caused the cerebral herniation.8–10

In adults with suspected meningitis, it is common to perform a computerized tomographic (CT) scan of the brain before doing an LP.11 This is because space-occupying lesions are common in adults, either tumors mimicking meningitis or intracranial suppurative complications of meningitis. In one study, 24% of adults had abnormal CT scans and 5% had a lesion with a mass effect.11 However, the value of routine LP
in adults has been disputed by a consensus group of Canadian neurologists.12

**Question** | In children with suspected meningitis, is CT scan of the brain a reliable predictor of raised intracranial pressure or impending cerebral herniation?

**Literature review** | We found five observational studies13–17 and two reviews18,19 of CT in childhood bacterial meningitis.

A prospective study of 41 children who had routine CT scans for bacterial meningitis found that CT scan showed sub-dural effusions in 8, focal cerebral infarcts in 5, and basal cistern pus in 1.13 Clinical management was not influenced by the CT findings, which failed to reveal any clinically significant abnormalities that were not suspected on neurologic examination.13

In another study, 5 of 14 children with imminent herniation had a normal CT scan.10 In a retrospective study of 30 children, CT was normal in 10, of whom 6 had clinical evidence of raised intracranial pressure (ICP).14

CT is useful in deciding which children with neurologic disease and suspected intracranial complications need surgery.13–17 CT scan does not exclude raised intracranial pressure and even imminent herniation,10,13,14 and most children with abnormal CT scans have neurologic signs which would contraindicate LP.18,19 Furthermore, there are growing concerns that CT scans of the brain may lead to long-term risk of malignancy:20,21 the estimated lifetime cancer mortality risk attributable to the radiation exposure from a CT scan of the brain in a 1-year-old is 0.07% or 1 in 1430.20 CT scans are useful in assessing children with suspected intracranial pathology, but only after treatment. Routine use of CT scans before LP looking for raised intracranial pressure or impending herniation or to exclude space-occupying lesions is contrary to the evidence and potentially harmful.

**We recommend not using routine CT scans before LP for children with suspected meningitis.**

**Delayed LP**

Concern has been expressed that it is increasingly common to treat children with suspected meningitis with empiric antibiotics without doing an immediate LP.22,23 Delaying LP risks making the wrong diagnosis and giving the wrong treatment.

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**Box 10.1 Contraindications to immediate lumbar puncture**

- focal neurologic signs
- papilledema
- rapidly deteriorating consciousness or obtundation (Glasgow Coma Score < 8)
- signs of raised intracranial pressure (falling pulse, rising BP, dilated or poorly reacting pupil[s])
- continuous seizure activity
- bleeding diathesis

[NB: LP should be delayed but performed as soon as the child is clinically stable]

---

Our recommended contraindications to immediate LP are given in Box 10.1. There is general consensus that LP should be delayed if the child is considered to have a high risk of cerebral herniation,1,9,10,24 and most of the contraindications reflect clinical findings associated with cerebral herniation.8–10 Some authors have quoted a modified Glasgow Coma Score (GCS) < 13 as a contraindication to LP, a figure which was also used in the Advanced Paediatric Life Support Manual produced by the RCPCH advisory committee.22,23 This cutoff figure for GCS may derive from an adult study, which defined GCS < 13 as one of a number of features associated with an abnormal CT scan, but did not comment on its predictive value.11 We could find no evidence to support using a cutoff GCS of 13 in children with suspected meningitis, and its use would contraindicate LP in most children with suspected meningitis.23 The rationale for using a GCS < 8 as the cutoff comes from a retrospective study,25 which found that children with GCS < 8 were more likely to die from coning than were those with GCS 8 or above (RR 4.6, 95% CI 1.1–35.8).

If it is decided to treat empirically with antibiotics without immediate LP, the LP should be performed as soon as the child is clinically stable, preferably within 2–3 days. Abnormal CSF white count, sugar, and protein usually persist this long in bacterial meningitis,1 and rapid bacterial tests (e.g., polymerase chain reaction [PCR] for *N. meningitidis*, and antigen detection for pneumococcus and Hib) may still be positive.
CSF examination

Organisms
A Gram’s iodine stain of CSF (Gram stain) demonstrates bacteria in 60–90% of patients with bacterial meningitis who have not received prior antibiotics, and has a specificity > 97%.26–28

CSF white count and differential
It is not safe to rely on total or differential CSF white count to distinguish bacterial meningitis from viral meningitis for management decisions. In untreated bacterial meningitis, the CSF white cell count is usually in the range of 1000–5000 cells/mm³ (1000–5000 × 10⁶ cells/L), although the range is <100 to >10,000 and rarely no white cells are found in the CSF.26–29 The total CSF white count in viral meningitis is lower on average, but there is considerable overlap.26–29 There is usually a neutrophil predominance in bacterial meningitis, but a neutrophil predominance is found in more than half of all cases of viral meningitis in the first 24 hours, and often persists.29 More concerning for decisions about withholding antibiotics, the CSF may show a lymphocyte predominance in Listeria meningitis and in partially treated bacterial meningitis.1,28 Treatment decisions based on the CSF white cell count and differential should be guarded.

CSF glucose and CSF/serum glucose ratio
The CSF glucose is usually low in bacterial meningitis, but the ratio of CSF and blood glucose is more sensitive and specific than absolute CSF glucose levels.26–30 A CSF/serum glucose ratio of 0.4 or less is 80% sensitive and 98% specific for bacterial meningitis in children >2 months old.26–30

CSF protein
The CSF protein is usually, but not always, >6 mg/dL (0.6 g/L) in bacterial meningitis.26–30 Very high CSF protein levels should raise suspicion of tuberculous meningitis.1

CSF lactate
CSF lactate level has been reported to be more sensitive and specific for bacterial meningitis than other CSF parameters.31–33 As with other parameters, however, the CSF lactate may be normal in bacterial meningitis. CSF lactate was also reported as being marginally more accurate than CSF/serum glucose ratio in patients with suspected bacterial meningitis post-neurosurgery.34

Rapid bacterial assays on CSF
PCR has been used to amplify nucleic acid from N. meningitidis, S. pneumoniae, Hib, S. agalactiae (GBS), and Listeria monocytogenes. The sensitivity and specificity of the different tests are in the range 90–98%. These tests can be used when the patient has received prior antibiotics and with infection with relatively fastidious organisms such as meningococcus.24,35,36 Latex agglutination tests are simpler and cheaper, but less sensitive37 and their routine use is not recommended.1,24 As with PCR, the main use is probably for pretreated patients.

Acute phase reactants
Serum and CSF CRP are often raised in bacterial meningitis. A meta-analysis of 21 studies of CSF CRP and 10 studies of serum CRP found a wide range in sensitivity (69–99%) and specificity (28–99%) of serum CRP to predict bacterial meningitis.38 The tests were most useful if they were negative, having >97% negative predictive value, but less useful to make a firm diagnosis of bacterial meningitis.

In a small study, plasma procalcitonin distinguished children with bacterial meningitis from viral meningitis.39

Treatment of bacterial meningitis
An algorithm for the assessment and early management of a child with suspected meningitis is given in Figure 10.1.

Antibiotics for bacterial meningitis

Neonates and infants under 3 months
For neonates and infants under 3 months, the likely organisms are the neonatal organisms, S. agalactiae, E. coli, other enteric Gram-negative rods, or Listeria, plus the organisms which cause meningitis in older children. The Gram stain will often help decide which antibiotic(s) to start (see Table 10.1), but for empiric therapy when the organism is unknown, we recommend:

- amoxi/ampicillin 50 mg/kg IV, 6-hourly PLUS cefotaxime 50 mg/kg IV, 6-hourly PLUS vancomycin 15 mg/kg IV, 6-hourly (not needed for early onset neonatal meningitis)
Bacterial meningitis suspected

Assess whether LP contraindicated:
- Focal neurological signs
- Papilledema
- Rapidly deteriorating consciousness or obtundation (GCS < 8)
- Signs of raised intracranial pressure (falling pulse, rising BP, dilated or poorly reacting pupil/s)
- Continuous fitting
- Bleeding diathesis

None of the above criteria

Blood cultures, LP and empirical treatment within 30 min of initial assessment

Dexamethasone 0.15 mg/kg (max 10 mg) IV PLUS empirical antibiotics IV

CSF findings consistent with bacterial meningitis

No

Reassess

Yes

Is Streptococcus pneumoniae suggested on Gram stain or antigen test?

No

Continue empirical therapy

Yes

Add vancomycin to empirical therapy

Any of the above criteria

Blood cultures and empirical treatment within 30 min of initial assessment

Dexamethasone 0.15 mg/kg (max 10 mg) IV PLUS empirical antibiotics IV

Do LP when no contraindication

Contraindication resolved

LP still contraindicated

Reassess and treat accordingly

Figure 10.1 Algorithm for management of suspected bacterial meningitis in children.
Table 10.1 Specific antibiotic therapy for neonates and babies <3 months old, according to CSF Gram stain.

<table>
<thead>
<tr>
<th>Gram Stain</th>
<th>Likely Organism</th>
<th>Suggested Antibiotic Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive cocci</td>
<td>Group B streptococcus, <em>Streptococcus faecalis</em>, <em>Streptococcus pneumoniae</em></td>
<td>Cefotaxime 50 mg/kg IV, 6-hourly PLUS vancomycin 15 mg/kg IV, 6-hourly</td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td><em>Escherichia coli</em>, <em>Salmonella</em>, other Gram-negative bacilli</td>
<td>Cefotaxime 50 mg/kg IV, 6-hourly OR cefepime 50 mg/kg IV, 8-hourly</td>
</tr>
<tr>
<td>Gram-negative cocci</td>
<td><em>Neisseria meningitidis</em></td>
<td>Benzylpenicillin 45 mg/kg IV, 4-hourly</td>
</tr>
<tr>
<td>Gram-positive bacilli</td>
<td><em>Listeria monocytogenes</em></td>
<td>Amoxi/ampicillin 50 mg/kg IV, 6-hourly</td>
</tr>
</tbody>
</table>

The third-generation cephalosporins are recommended because of excellent CSF penetration, rapid CSF sterilization, and because of activity against Gram-negative bacilli as well as some Gram-positive organisms. Ceftriaxone is not recommended for neonates because it can displace bilirubin from albumin and because it can cause biliary sludging. Ampicillin or amoxicillin is added to the third-generation cephalosporins because the latter have no activity against *Listeria* or enterococci.

Cefotaxime has no activity against *Pseudomonas*. If *Pseudomonas* is suspected to be the cause of meningitis, e.g., because of prior colonization, cefepime (or ceftazidime or meropenem) is recommended.

Vancomycin is used because of the increasing number of cases of infection with *S. pneumoniae* which are relatively insensitive to penicillin. The recommendation to use vancomycin is based on convincing clinical descriptions of children with meningitis due to penicillin-insensitive pneumococci who do not improve until vancomycin is started. There are no prospective studies comparing vancomycin with other treatments in this situation, but in one retrospective study children with penicillin-insensitive pneumococcal meningitis given vancomycin required shorter duration of treatment than those not given vancomycin.

Children 3 months and older

For children >3 months old, the likely organisms and the recommended treatment are shown in Table 10.2. The frequency of organisms depends on local epidemiology and on immunization practices. *Listeria meningitis* is rare outside the neonatal period, but, if it does occur, is usually in immunodeficient children.

For empiric therapy, when the organism is unknown, we recommend:

- **vancomycin 15 mg/kg (max 500 mg) IV, 6-hourly PLUS EITHER**
- **cefotaxime 50 mg/kg (max 2 g) IV, 6-hourly OR ceftriaxone 50 mg/kg (max 2 g) IV, daily**

We recommend stopping the vancomycin if a penicillin-susceptible pneumococcus (minimum inhibitory concentration [MIC] <0.125 mg/L) or another organism likely to be susceptible to ceftriaxone/cefotaxime is grown.

Table 10.2 Specific antibiotic therapy for children 3 months old and older, according to CSF Gram stain.

<table>
<thead>
<tr>
<th>Gram Stain</th>
<th>Likely Organism</th>
<th>Suggested Antibiotic Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive cocci</td>
<td><em>Streptococcus pneumoniae</em></td>
<td>Cefotaxime 50 mg/kg (max 2 g) IV, 6-hourly PLUS vancomycin 15 mg/kg (max 600 mg) IV, 6-hourly</td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td><em>Haemophilus influenzae</em></td>
<td>Cefotaxime 50 mg/kg (max 2 g) IV, 6-hourly OR ceftriaxone 50 mg/kg (max 2 g) IV, daily</td>
</tr>
<tr>
<td>Gram-negative cocci</td>
<td><em>Neisseria meningitidis</em></td>
<td>Benzylpenicillin 45 mg/kg (max 1.8 g) IV, 4-hourly</td>
</tr>
<tr>
<td>Gram-positive bacilli</td>
<td><em>Listeria monocytogenes</em></td>
<td>Amoxi/ampicillin 50 mg/kg (max 2 g) IV, 6-hourly</td>
</tr>
</tbody>
</table>
For patients with anaphylactic penicillin or cephalosporin allergy, we recommend:

**vancomycin 15 mg/kg (max 500 mg) IV, 6-hourly**
**PLUS EITHER**
**ciprofloxacin 15 mg/kg (max 600 mg) IV, 12-hourly OR**
**moxifloxacin 10 mg/kg (max 400 mg) IV, daily**

Subsequent therapy is guided by cultures and other tests.

If meningococcal meningitis and/or septicemia is suspected, e.g., because of a purpuric rash, emergency treatment with parenteral benzylpenicillin before hospital admission is recommended (see p. 249).

**Corticosteroids for bacterial meningitis**

**Question** | In children with bacterial meningitis, does adjunctive therapy with corticosteroids compared with no corticosteroids or placebo reduce morbidity or mortality?

**Literature review |** We found 21 RCTs and a Cochrane review of corticosteroids and bacterial meningitis.45

The Cochrane review found 18 RCTs (1853 adults and children) of corticosteroid therapy and bacterial meningitis.45 Overall, adjuvant corticosteroids were associated with lower case fatality (RR 0.76, 95% CI 0.59–0.98) and lower rates of both severe hearing loss (RR 0.36, 95% CI 0.22–0.60) and long-term neurologic sequelae (RR 0.66, 95% CI 0.44–0.99). However, the meta-analysis was dependent mainly on *H. influenzae* meningitis, which used to be the commonest cause of childhood meningitis but has virtually disappeared post-immunization.1

Corticosteroids reduced severe hearing loss in children with *H. influenzae* meningitis (RR 0.31, 95% CI 0.15–0.62) and in meningitis caused by bacteria other than *H. influenzae* (RR 0.42, 95% CI 0.20–0.89). For meningitis caused by bacteria other than *H. influenzae*, 20 children would need to be treated with corticosteroids to prevent one case of hearing loss.45 The numbers of cases were insufficient to say that corticosteroids reduced hearing loss for any particular organism, except *H. influenzae*.

There was no demonstrated reduction in mortality for pneumococcal meningitis, although a subsequent, retrospective Australian study46 found that use of corticosteroids before or with parenteral antibiotics was associated with reduced chance of death or severe morbidity from pneumococcal meningitis (adjusted OR 0.21, 95% CI 0.05–0.77). A study from Malawi found no benefit from dexamethasone in children with bacterial meningitis, suggesting that corticosteroids are not beneficial in a developing country setting, where HIV coinfection is likely to be important.47

In a subsequent adult study,48 treatment with dexamethasone was associated with a reduction in mortality (RR 0.48, 95% CI 0.24–0.96) and a halving of poor neurologic outcome from 52 to 26% of cases (RR 0.50, 95% CI 0.30–0.83).

The two major concerns about corticosteroid therapy are whether it is associated with an increased risk of gastrointestinal bleeding and whether corticosteroid therapy might delay sterilization of the CSF, particularly for penicillin-insensitive pneumococci. The Cochrane meta-analysis45 and subsequent adult study48 found no increase in gastrointestinal bleeding in association with corticosteroids. There are insufficient data on whether or not dexamethasone therapy delays CSF sterilization in meningitis due to penicillin-insensitive pneumococci.44

We believe the evidence favors early treatment with dexamethasone, given before or with the first dose of antibiotic, for children with haemophilus or pneumococcal meningitis. We feel there are insufficient data on corticosteroids for meningococcal meningitis to recommend their routine use (see p. 250), although there is no evidence to suggest they are harmful either. For children with presumed meningitis who are treated empirically without an immediate LP and for children with CSF pleocytosis but no organism seen, we recommend corticosteroids. Data suggest there is no benefit in commencing corticosteroids after the first dose of antibiotic.

**We recommend giving dexamethasone just before or with the first dose of antibiotic for children with proven or presumed meningitis (other than meningococcal meningitis).**

We recommend:

**dexamethasone 0.15 mg/kg (max 10 mg) IV, before or with the first dose of antibiotic, then 6-hourly for 4 days.**
If dexamethasone is unavailable, we recommend using hydrocortisone 4 mg/kg (max 200 mg) IV for the initial dose.

**Intravenous fluids for bacterial meningitis**

**Question** | In children with bacterial meningitis, does fluid restriction compared with no fluid restriction improve outcome?

**Literature review** | We found six studies of which three were retrospective and three were RCTs, and a Cochrane review of fluid therapy for bacterial meningitis.49

The serum sodium is often low and urine output decreased in bacterial meningitis. For a long time, this was thought to be due to the syndrome of inappropriate antidiuretic hormone secretion, and fluid restriction was recommended for children with bacterial meningitis. This belief has been questioned, and biochemical evidence has been presented that the low urine output and low sodium are due to fluid depletion.50 Some have even suggested that hyponatremia in treated children is due to the ”syndrome of inappropriate fluids.”

A Cochrane review found three RCTs from the USA, India, and Papua New Guinea (PNG) which compared maintenance fluids (normal fluid replacement) with fluid restriction.49 Mortality was high in the PNG study, which was the largest of the three. The meta-analysis found no significant difference between the maintenance-fluid and restricted-fluid groups in number of deaths (RR 0.82, 95% CI 0.53–1.27), acute severe neurologic sequelae (RR 0.67, 95% CI 0.41–1.08), or in mild to moderate sequelae (RR 1.24, 95% CI 0.58–2.65). However, children given maintenance fluids were less likely to develop spasticity (RR 0.50, 95% CI 0.27–0.93), to have seizures at both 72 hours (RR 0.59, 95% CI 0.42–0.83) and 14 days (RR 0.19, 95% CI 0.04–0.88), and to have chronic severe neurologic sequelae at 3-months follow-up (RR 0.42, 95% CI 0.20–0.89).49

**We do not recommend fluid restriction for children with bacterial meningitis.**

**Duration of antibiotics for bacterial meningitis**

The duration of therapy for bacterial meningitis is dictated more by custom than by evidence.51,52 The numbers of days of antibiotics given in studies tend to be multiples of “magical numbers,” the number of fingers on a hand (5) or days in a week (7).51

It has been known for over 30 years that meningococci are extremely sensitive to antibiotics and meningococcal meningitis can be cured with a single dose of long-acting penicillin53 or chloramphenicol.54 Treatment of bacterial meningitis, from whatever organism, was, nevertheless, traditionally for at least 10–14 days, and longer if fever persisted or for neonatal meningitis. It was then shown that for children >3 months old who were making an uncomplicated recovery, 7 days treatment with ceftriaxone was as good as 10 days.55 A study in Chile showed that 4 days of ceftriaxone was equivalent to 7 days for selected children who were improving rapidly56 (the choice of 4 rather than 5 days contradicted the magical numbers theory).

Our recommendations for antibiotic duration are based on the current Infectious Disease Society of America consensus recommendations11 and are shown in Table 10.3. The evidence base is poor, and any individual child may need to be treated longer if fever persists. We do not recommend using oral antibiotics for any of the course, because oral antibiotics are unlikely to achieve adequate CSF levels to sterilize the CSF.

**Table 10.3 Recommended duration of parenteral antibiotics for uncomplicated meningitis in children.**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Duration of Antibiotics (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Neisseria meningitidis</em></td>
<td>5</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>7</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>10</td>
</tr>
<tr>
<td>Group B streptococcus</td>
<td>14–21</td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td>21</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td>21</td>
</tr>
</tbody>
</table>

**Chemoprophylaxis in bacterial meningitis**

The secondary attack rate in household contacts is increased to 4.2 per 1000 for meningococcal disease57 and to 5.2 per 1000 for Hib.58 Antibiotic prophylaxis is recommended to prevent secondary cases of bacterial meningitis in household contacts of patients with meningitis due to *N. meningitidis* (see p. 251) or Hib. How strong is the evidence?
Question | For household contacts of patients with bacterial meningitis due to meningococcus or Hib, do prophylactic antibiotics compared with no antibiotics or placebo prevent secondary cases?

Literature review | We found a non-Cochrane systematic review[^59] and a Cochrane review of prophylactic antibiotics in meningococcal infection[^60] and a case-control study in Hib infection[^58].

A non-Cochrane systematic review of the effectiveness of prophylactic antibiotics in meningococcal infection[^59] found no high-quality prospective studies, but four retrospective observational studies and one small trial comparing children who did or did not receive chemoprophylaxis. The outcome was secondary cases of meningococcal infection occurring 1–30 days after the index case. Chemoprophylaxis reduced the risk of meningococcal infection for household contacts by an impressive 89%: the risk ratio was 0.11 (95% CI 0.02–0.58) and 218 contacts had to take prophylactic antibiotics to prevent one case of meningococcal infection. In contrast, the data in day-care settings were insufficient to judge whether or not chemoprophylaxis is indicated.

A Cochrane review of chemoprophylaxis[^60] found no RCTs and no secondary cases, so could not comment on the effectiveness of chemoprophylaxis. It found that ciprofloxacin, minocycline, and rifampicin were effective at eradicating nasal carriage of meningococcus at 1 week, but only rifampin (RR 0.20, 95% CI 0.14–0.29) and ciprofloxacin (RR 0.03, 95% CI 0.00–0.42) still proved effective at 1–2 weeks. Rifampin continued to be effective compared to placebo for up to 4 weeks after treatment but resistant isolates were seen following prophylactic treatment. No trials evaluated ceftriaxone against placebo but ceftriaxone was more effective than rifampin after 1–2 weeks of follow-up (RR 5.93, 95% CI 1.22–28.68).

Because there were no cases of meningococcal disease during follow-up in any of the trials, effectiveness regarding prevention of future disease cannot be directly assessed.

We recommend *N. meningitidis* (meningococcus) prophylaxis for household contacts using:

**rifampicin**: neonate <1 month 10 mg/kg; child 10 mg/kg (max 600 mg), adult 600 mg, orally, 12-hourly for 2 days (preferred option for children) OR

**ciprofloxacin** (adult and child ≥12 years) 500 mg orally, child 12.5 mg/kg (max 500 mg) as a single dose OR

**ceftriaxone** 250 mg (child: 125 mg) IM as a single dose (preferred option during pregnancy).

Rifampicin is associated with multiple drug interactions, stains contact lenses orange, and is not recommended for persons with severe liver disease. Because they cause cartilage damage in laboratory animals, there are theoretical concerns about quinolones causing skeletal problems in children, although data do not suggest this is a real clinical problem[^61].

A case-control study showed that chemoprophylaxis of household contacts not only reduces carriage of Hib, but appears to prevent secondary cases of Hib disease[^58]. Hib disease is rare in countries that routinely use Hib conjugate vaccines. If a case of Hib disease occurs in a well-immunized population, chemoprophylaxis is indicated only if there is an unimmunized or partially immunized child in the household, i.e., any baby 6 months of age or less or else a child <5 years old who is not fully immunized. In that case and in unimmunized populations, prophylaxis should be given to the whole family to reduce the risk of transmission. We recommend:

**rifampicin**: neonate <1 month 10 mg/kg; child 20 mg/kg (max 600 mg), adult 600 mg orally, daily for 4 days

**Skull fracture and bacterial meningitis**

Skull fractures, particularly fractures of the base of the skull, predispose to bacterial meningitis if the dura mater adjacent to the fracture site is torn, placing the central nervous system (CNS) in contact with bacteria from the paranasal sinuses, nasopharynx, or middle ear. A greater associated risk has been reported when CSF leakage occurs, particularly if it persists for more than 7 days[^62].

Question | In patients with post-traumatic CSF leak, do prophylactic antibiotics compared with no antibiotics reduce the risk of bacterial meningitis?

Literature review | We found five RCTs, two non-Cochrane meta-analyses[^63,64] and a Cochrane review[^65].

In one non-Cochrane meta-analysis of patients with post-traumatic CSF leak, the risk of bacterial meningitis was 2.5% if they received antibiotics.
and 10% if they did not, and the difference was significant. Another non-Cochrane meta-analysis and a Cochrane review, however, found the incidence of meningitis with or without antibiotics was 6–7%, with no demonstrable benefit from prophylactic antibiotics.

We do not recommend prophylactic antibiotics for children with post-traumatic CSF leak.

Recurrence bacterial meningitis
For children with recurrent bacterial meningitis, the major causes are anatomic or immunologic abnormalities. Anatomic abnormalities include an occult dural lesion such as a dermal sinus tract, basal encephalocele, or neurenteric cyst, and so physical examination should include a careful search along the craniospinal axis, proceeding to diagnostic imaging (MRI or CT) if there is any suspicion. Abnormalities of the inner ear, such as Mondini dysplasia, are usually associated with CSF leak which can be occult. The diagnosis is made by performing thin-cut computed tomography of the temporal bones. Basal skull fractures, usually post-traumatic and associated with CSF leak, should also be considered (see p. 139).

Immunologic abnormalities that should be considered include humoral defects (measure total serum immunoglobulins and consider measuring functional antibody levels to immunizations, such as Hib or pneumococcus) and complement defects. Terminal complement defects are associated with recurrent meningococcal infection. Asplenia predisposes to infection with capsulated organisms (see Section 9.3, p. 125) but is an unusual cause of recurrent meningitis.

The organism responsible for the recurrent bacterial meningitis may be significant. Pneumococcus or Haemophilus suggests cranial dural defects, E. coli or other Gram-negative bacilli suggest spinal dural defects, and meningococci suggest complement deficiency or IgM deficiency.

Recurrence of acute bacterial meningitis due to persistence and recrudescence of the causative organism is more common in neonates than in older children, and may or may not be due to an intracranial collection, such as brain abscess. Antibiotic-induced meningitis (usually due to penicillin or trimethoprim-sulfamethoxazole or intrathecal antibiotics) is a rare cause of recurrent aseptic meningitis. Finally, if there are puzzling aspects of the recurrent meningitis, such as different organisms or failure to respond to apparently adequate treatment, the possibility of Munchausen syndrome by proxy may need to be considered.

Cochlear implants and bacterial meningitis
Cochlear implants are medical devices that electronically stimulate the auditory nerves in the cochlea (inner ear), allowing persons with severe hearing loss to perceive sound. In 2002, a cluster of cases of bacterial meningitis was identified among European cochlear implant recipients. Although there was initial suspicion that this was related to one manufacturer and one device, subsequent epidemiologic studies have revealed that the risk of bacterial meningitis for cochlear transplant recipients is increased. In particular, the risk of pneumococcal meningitis is more than 30 times the expected incidence for age in the USA. The risk is also increased in Canada. Although the largest increase by far is for pneumococcal meningitis, there have also been anecdotal reports of meningitis with H. influenzae (both type b and untypeable), N. meningitidis, Enterococcus, Acinetobacter baumanii, and E. coli. Almost all cochlear implant devices are associated with an increased risk of pneumococcal meningitis, although the presence of an extra piece called a “positioner,” which holds the electrode in place, greatly increases the risk.

In countries with universal infant pneumococcal immunization, it is sufficient to ensure that all children who receive cochlear implants are routinely immunized and are monitored and treated promptly for any bacterial infections after receiving the implant. In countries without universal infant pneumococcal immunization, children with cochlear implants should be immunized as for children with asplenia (see p. 126).

CNS shunt infections
Ventricular shunts are used frequently to treat congenital or post-hemorrhagic hydrocephalus in newborns and to treat various causes of hydrocephalus in older children. The reported incidence of shunt infection varies widely from 1.5 to 39%, although more recently rates of 10–15% have been reported. In a
retrospective review of patients undergoing CSF shunt operations between 1996 and 1999, three perioperative variables were significantly associated with an increased risk of shunt infection: prematurity, the presence of a post-operative CSF leak, and inadvertent exposure to breached surgical gloves.78

The most common pathogens are coagulase-negative staphylococci (50–90%), followed by Staphylococcus aureus (13–27%), and a miscellany of other organisms, including aerobic Gram-negative bacilli (10–20%), streptococci (8–10%), and Propionibacterium spp.76–78 Coagulase-negative staphylococci are known to produce a glycocalyx (slime layer), which allows them to survive on the surface of synthetic materials as in shunts and makes it hard to sterilize the shunt with antibiotics.79

Babies and older children with CSF shunt infections may present with the acute signs and symptoms of meningitis. More commonly, however, they present more indolently with fever and irritability. The diagnosis is made by obtaining CSF for microscopy and culture. In one study, the serum CRP was elevated in 97.1% of children with CSF shunt infections, with a specificity of 73.5%.80 CRP may help identify which children are unlikely to be infected, but for optimum management there is no substitute for obtaining CSF.

The options for managing patients with shunt infections76–78 include:
(A) removal of the entire colonized shunt, external CSF drainage, either by implantation of an external ventricular drain or by regularly tapping the ventricles, administration of antibiotics systemically, intraventricularly, or both, and shunt replacement when the CSF is sterile;
(B) removal of the entire colonized shunt and immediate replacement with a new shunt, followed by a course of antibiotics (either systemic, intraventricular, or both);
(C) antibiotic therapy alone, administered either systemically, intraventricularly, or by both routes.

Variations on these options, with exteriorization of the distal shunt catheter and the administration of systemic and intraventricular antibiotics for between 2 and 4 weeks, followed by revision of either the distal catheter alone or the entire shunt system, have also been described.78

A single, small RCT compared patients who received each of options A, B, or C above.81 All 10 patients in Group A and 9 of 10 in Group B were treated successfully. In contrast, only 3 of 10 in Group C responded to antibiotic treatment without shunt removal.81 A recent observational paper reports that some adult patients with CSF shunts have been treated successfully with antibiotics alone.77 In general, however, the evidence suggests most infections in neonates and older children will not resolve without shunt removal.

There is debate on the relative merits of the intravenous and intraventricular routes of antibiotic administration, but few data. An RCT comparing vancomycin treatment of drain-associated staphylococcal ventriculitis in adults found that much higher CSF vancomycin levels were obtained using intraventricular than using intravenous treatment.82 Intraventricular treatment, however, cleared infection as well as intraventricular treatment. Intraventricular treatment also carries the risk of causing CNS damage through direct toxicity or through inflammatory changes consequent on endotoxin-induced cytokine release.83 A neonatal RCT found that neonates who received intraventricular gentamicin in addition to intravenous antibiotics compared to those receiving intravenous antibiotics alone had no shorter duration of positive cultures and had increased mortality (RR 3.43, 95% CI 1.09–10.74).84,85 We do not recommend giving intraventricular antibiotics unless the CSF cannot be sterilized using shunt removal, external drainage, and intravenous antibiotics.

Treatment should be based on CSF microscopy and culture. If for some reason cultures cannot be obtained or are delayed, we recommend the following empiric regimen, aimed at staphylococcal and Pseudomonas infection. The regimen should be modified, if necessary, as soon as Gram stain and culture results are available.

vancomycin 15 mg/kg (max 500 mg) IV, 6-hourly PLUS EITHER
ceftazidime 50 mg/kg (max 2 g) IV, 8-hourly OR
meropenem 40 mg/kg (max 2 g) IV, 8-hourly

Meropenem is preferred to imipenem–cilastatin due to the lower risk of seizures.86

There is interest in the use of antibiotic-impregnated shunt materials to reduce the risk of infection, but as yet insufficient data to recommend them.87
10.2 Subdural empyema

Subdural empyema in children usually occurs as a complication of meningitis, sinusitis, or mastoiditis. The incidence is biphasic in immunocompetent children, with cases either occurring in children <2 years mainly as a complication of bacterial meningitis, or in children >7 years mainly as a complication of sinusitis. The most frequent organism isolated from sinusitis-associated sub-dural empyema is \( \text{S. anginosus (milleri)} \), but polymicrobial infection with \( \text{S. pneumoniae, S. aureus, Gram-negative bacilli, and anaerobes is common.} \) A distinction is sometimes drawn between sub-dural empyema and intracranial epidural abscess, but is not always easy to make in practice.

Although there are anecdotal reports of medical treatment of sub-dural empyema with antibiotics alone, neurosurgical exploration is strongly advised, both for treatment and to identify the causative organisms.

For empiric antibiotic treatment, we recommend:

- **benzylpenicillin 60 mg (100,000 U)/kg (max 3.6 g or 6 million U) IV, 4-hourly PLUS**
- **metronidazole 12.5 mg/kg (max 500 mg) IV, 8-hourly PLUS**
- **cefotaxime 50 mg/kg (max 2 g) IV, 6-hourly**

10.3 Brain abscess

The term *brain abscess* refers to an abscess within the brain parenchyma, as opposed to a sub-dural empyema or an intracranial epidural abscess, which are both extra parenchymal.

We found no RCTs on the treatment of brain abscess in children, but we found observational studies on treatment and outcome, and a review on the management of brain abscess in children.

Almost 25% of all brain abscesses occur in children <15 years, with a peak at 4–7 years. The most common predisposing conditions are cyanotic congenital heart disease (hematogenous spread) and direct spread from a contiguous site (middle ear, sinuses, teeth). Brain abscesses are uncommon complications of bacterial meningitis or head trauma (usually with a significant delay from the time of injury). Although conditions such as cystic fibrosis, bronchiectasis, and brain surgery predispose to brain abscess, no predisposing factor can be identified in up to 30% of children.

Aerobic and anaerobic streptococci, including \( \text{S. anginosus (milleri)} \) are grown from 50 to 70% of brain abscesses in children. However, where the likely site of origin is the ear, enteric Gram-negative bacilli are commonly involved (10–25% of all abscesses), while after trauma or surgery, staphylococci predominate (10–30% of total). Polymicrobial infection, often involving anaerobic organisms, is found in up to 30% of children. In neonates, Gram-negative enteric bacilli are most common. Immuno compromised hosts can develop brain abscesses caused by *Nocardia*, by fungi such as *Aspergillus* or *Scedosporium*, or by *Mycobacterium tuberculosis*. *Toxoplasma gondii*, a common cause of parasitic brain abscess in adults with AIDS, is rarely encountered in children.

The clinical presentation of brain abscess in infants and children varies depending on the location of the abscess or abscesses, the virulence of the organism and the child’s immune status. Headache, fever, and vomiting each occur in 60–70%. Seizures, altered mental status, and focal neurologic signs occur in 25–50%. Meningeal signs occur in <25% and the classic triad of fever, headache, and focal deficits occurs in <30% of children. Thus the clinical features are often nonspecific and a high index of suspicion is required.

Routine laboratory tests are often unhelpful. The CSF may show a pleocytosis, but no organisms are seen and culture is sterile. Other CSF parameters do not distinguish brain abscess from bacterial or aseptic meningitis. Positive blood cultures are found in about 10% of cases. If brain abscess is suspected clinically, imaging with CT and/or MRI (magnetic resonance imaging) is indicated. If imaging studies indicate a brain abscess, LP is generally not indicated because of the low yield.

CT and MRI are the most important diagnostic tools. MRI is superior to CT because of greater sensitivity and better soft tissue details. CT scan with contrast may show a hypodense, ring-enhancing lesion. Because the CT appearances develop slowly and may lag behind the clinical presentation, a normal CT scan does not exclude a brain abscess.

Aspiration or biopsy can guide antimicrobial therapy and is often important for treatment, because antibiotics penetrate relatively poorly into the brain tissue.
For brain abscess associated with sinusitis, mastoiditis, otitis, or cyanotic congenital heart disease, we recommend:

- **metronidazole 12.5 mg/kg (max 500 mg) IV, 8-hourly PLUS EITHER**
- **cefotaxime 50 mg/kg (max 2 g) IV, 6-hourly OR ceftriaxone 100 mg/kg (max 4 g) IV, daily**

For post-neurosurgical brain abscess, penetrating head trauma, ventriculoperitoneal shunts, or endocarditis where the risk of *S. aureus*, MRSA, and coagulase negative staphylococcal infection is much greater, and for abscesses associated with meningitis, to cover penicillin-insensitive *S. pneumoniae*, we recommend:

- **vancomycin 15 mg/kg (max 500 mg) IV, 6-hourly PLUS EITHER**
- **cefotaxime 50 mg/kg (max 2 g) IV, 6-hourly OR ceftriaxone 100 mg/kg (max 4 g) IV, daily**

If microscopy and/or culture indicates the need to cover for *Pseudomonas aeruginosa*,

96–99 we recommend using instead of cefotaxime or ceftriaxone:

- **ceftazidime 50 mg/kg (max 2 g) IV, 8-hourly OR meropenem 40 mg/kg (max 2 g) IV, 8-hourly**

In neonatal brain abscess, where *L. monocytogenes* is possible, ampicillin should be used with cefotaxime, as on p. 134.

For empiric therapy, if aspiration cannot be performed, we recommend:

- **benzylpenicillin 60 mg (100,000 U)/kg (max 3.6 g or 6 million U) IV, 4-hourly PLUS**
- **metronidazole 12.5 mg/kg (max 500 mg) IV, 8-hourly PLUS EITHER**
- **ceftriaxone 100 mg/kg (max 4 g) IV, daily OR cefotaxime 50 mg/kg (max 2 g) IV, 6-hourly**

Therapy should be modified on the basis of Gram stain and culture results. The optimum duration of treatment is unknown and should be individualized, based on clinical response and radiologic evidence of resolution. Intravenous antibiotics generally should be continued for 4–6 weeks, although a 3–4-week course may be adequate for those who underwent surgical excision. After this time, small residual abscesses may remain but clinical data suggest they are sterile. Some authorities recommend an additional 2–3 months of oral antibiotics, but the benefit is doubtful. Corticosteroids may decrease intracranial pressure but are not routinely recommended because of concerns that they can also decrease antibiotic penetration across the blood–brain barrier and impair clearance of pathogens.94

### 10.4 Spinal epidural abscess

Spinal epidural abscess presents with fever, back pain, diminished movement in the legs (paraplegia or paraparesis), and sometimes urinary retention.96 Spinal epidural abscesses are frequently associated with adjacent vertebral osteomyelitis or disc infection, and are most likely to be caused by *S. aureus*. The major differential diagnosis is transverse myelitis (see Section 10.13, p. 149).

Spinal epidural abscess is a surgical emergency, especially if associated with neurologic deficit. Immediate radiologic assessment is a priority, because of the risk of progressive neurologic damage with epidural abscess. Magnetic resonance imaging is the best and only reliable non-invasive method for assessing the epidural space and spinal cord. T1-gadolinium sequences will show an epidural mass with peripheral enhancement.96

If radiology suggests an epidural abscess, emergency surgical assessment with a view to drainage of the epidural collection is essential. A retrospective study of adults with spinal epidural abscess, mainly lumbar, reported that the outcome was the same in patients treated with surgery plus antibiotics, CT-guided aspiration plus antibiotics, or antibiotics alone.97 Most authorities advocate surgical or radiologic drainage because of the risk of cord compression leading to irreversible neurologic damage,96 although a severity grading system might allow conservative medical management of patients at low risk for neurologic damage.98 Antibiotic treatment should be based on the Gram stain and culture results of operative material, but for empiric therapy prior to surgery, we recommend:

- **di/flucl/oxa/nafcillin 50 mg/kg (max 2 g) IV, 6-hourly PLUS**
- **gentamicin <10 years: 7.5 mg/kg; ≥10 years: 6 mg/kg IV, daily**

Where MRSA infection is likely, because of ethnicity (community-acquired MRSA) or previous colonization or prolonged hospital exposure (hospital-acquired
MRSA), and for patients with anaphylactic penicillin or flucloxacinill allergy, we recommend:

vancomycin 12.5 mg/kg (max 500 mg) IV,
6-hourly PLUS
gentamicin <10 years: 7.5 mg/kg; ≥10 years:
6 mg/kg IV, daily

Clindamycin is a possible alternative to vancomycin when community-acquired MRSA infection is suspected. The duration of therapy is empiric, but we suggest at least 3 weeks, as for osteomyelitis.

Aseptic meningitis
There are a number of reasons that the CSF might be sterile despite evidence of inflammation from raised CSF white cells (CSF pleocytosis). Some examples are given in Box 10.2.

**Box 10.2 Causes of CSF pleocytosis with sterile CSF.**

- Bacterial meningitis, but no growth
- Partially treated meningitis (prior antibiotics)
- Parameningeal infections, i.e., infection next to meninges (e.g., brain abscess, sub-dural empyema)
- Viral meningitis
- Viral encephalitis, including HSV encephalitis
- Mycoplasma meningoencephalitis
- Acute disseminated encephalomyelitis
- Lyme meningitis
- Tuberculous meningitis
- Fungal meningitis
- Bacterial endocarditis
- Inflammatory, e.g., SLE
- Malignancy
- Drugs, including parenteral and intrathecal antibiotics

### 10.5 Viral meningitis

**Clinical features of viral meningitis**

Because of the treatment implications, the major diagnoses to consider in a child with suspected viral meningitis are bacterial meningitis and herpes simplex virus (HSV) encephalitis. Other conditions in Box 10.2 may warrant consideration depending on the clinical situation.

Children with viral meningitis are usually but not always less sick than children with bacterial meningitis, but for any individual child the clinical examination is neither sensitive nor specific enough to determine the need for LP or to suggest it is safe to withhold therapy.26–28 HSV can either cause a benign viral meningitis or the much more sinister HSV encephalitis, which will be considered separately in Section 10.7 (p. 145). Children with HSV meningitis may have neck stiffness, headache, and fever, but no significant alteration in level of consciousness and no focal neurologic signs.99 In contrast, children with HSV encephalitis usually present with one or more of focal or generalized seizures, which often become intractable, decreased level of consciousness, aphasia or neurobehavioral changes, cranial nerve palsies, visual field defects or weakness, which may be hemiplegic or generalized.99

A macular or maculopapular rash may occur in enterovirus infections, but children with meningococcal infection can also present with an identical rash,100 and so the presence of a rash in a child with meningism does not mean it is necessarily safe to withhold antibiotics.

**CSF microscopy and biochemistry in viral meningitis**

The CSF total white count, neutrophil count, and glucose, protein, lactate, or CRP levels may strongly suggest viral rather than bacterial meningitis, but, as discussed on p. 134, have insufficient sensitivity to withhold antibiotics from a child with meningism and CSF pleocytosis.26–33 Models based on CSF parameters have been developed which differentiate bacterial meningitis from viral meningitis accurately, but still miss occasional cases of bacterial meningitis.101,102 It is potentially dangerous to withhold antibiotics on the basis of such a model.

**CSF PCR testing in viral meningitis**

The use of rapid viral tests, such as PCR on CSF, can help with decisions about treatment, particularly the decision whether it is safe to cease antimicrobial therapy for a child with aseptic meningitis, if PCR results are available in a timely fashion. A review found that enterovirus PCR has >90% sensitivity compared with virus isolation for detecting the enteroviruses: Coxsackie, echo, and polioviruses.103 The same review
also reported that HSV PCR has >90% sensitivity.\textsuperscript{103} Mumps is the commonest cause of viral meningitis in unimmunized populations, and outbreaks of mumps are even described despite widespread immunization. Mumps PCR also has a specificity >90%.\textsuperscript{103}

Whenever possible when managing a child with suspected viral meningitis, we recommend culturing CSF for viruses (enteroviruses, HSV, and mumps) and sending CSF for PCR to detect enteroviruses and HSV.

### Viral culture in viral meningitis

Viral culture of CSF has largely been superseded by PCR in many laboratories, because PCR for enteroviruses and HSV is >90% sensitive and is quicker. When PCR is unavailable, viral culture can still provide valuable information and although enteroviruses grow slowly, HSV cultures may be positive after 2–3 days.\textsuperscript{99,104}

### Serology in viral meningitis

Serology is rarely helpful for enteroviral infections: children do not mount a detectable antibody response and the tests have poor sensitivity compared with PCR or culture. In one study of children with enteroviral meningitis diagnosed by CSF PCR, 34% had serum IgM to enteroviruses and only 20% had a positive complement fixation test.\textsuperscript{105}

Serology may be informative in HSV meningitis or meningoencephalitis, but mainly for making a retrospective diagnosis rather than helping with acute management.\textsuperscript{99,104}

### Treatment of viral meningitis

The treatment of viral meningitis is primarily supportive, with the exception of HSV encephalitis (see Section 10.7, p. 145). Pleconaril is an antiviral with in vitro activity against enteroviruses, it has some therapeutic efficacy in enteroviral respiratory infections in adults, and there are anecdotal reports of its use in severe enteroviral infections, including meningitis.\textsuperscript{106} A double-blind placebo-controlled trial of pleconaril in 20 infants with enteroviral meningitis found no benefit in terms of viral shedding or any clinical outcomes, despite adequate drug levels.\textsuperscript{107} Furthermore, there was evidence of drug accumulation and the treatment group had twice as many adverse events.\textsuperscript{107}

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### 10.6 Viral encephalitis

The incidence of acute viral encephalitis in childhood is about 10 per 100,000 and up to 30 per 100,000 infants <1 year old.\textsuperscript{108–110} It is possible to identify an agent in 40–75% of cases: enteroviruses, \textit{Mycoplasma pneumoniae}, HSV, and influenza are the commonest in recent studies, but arthropod-borne viruses such as West Nile virus and Japanese encephalitis virus are important in some regions.\textsuperscript{108–110}

If a child presents with signs and symptoms suggestive of encephalitis, the main priority after resuscitation is to investigate for HSV encephalitis and to treat with acyclovir if there is any doubt. Many experts recommend empiric treatment with acyclovir of all children with acute encephalitis pending further results.\textsuperscript{111}

We recommend starting acyclovir for a child with acute encephalitis and continuing until HSV infection has been excluded.

### 10.7 HSV encephalitis

The annual incidence of HSV encephalitis in the USA is about 20–50 per 100,000 neonates and 3 per 100,000 older children.\textsuperscript{108–111} The diagnosis is clinical, supported by laboratory criteria and by imaging. PCR on CSF for HSV nucleic acid is >90% sensitive and specific compared with brain biopsy, and brain biopsy is almost never performed nowadays.\textsuperscript{108–111} In neonates, CSF PCR has lower reported sensitivity, at 74–93%.\textsuperscript{61} Serology is mostly unhelpful in the acute phase, but serum should be sent to look for specific IgM and IgG to HSV-1 and HSV-2.\textsuperscript{102} Support for a diagnosis of HSV encephalitis can be provided by finding focal changes on the EEG or by cerebral imaging using CT scan or MRI scan, all of which characteristically show temporal lobe damage.\textsuperscript{99,104} Temporal lobe involvement is sensitive, suggestive MRI changes being found in 90% of patients,\textsuperscript{99} but is non-specific since similar changes can occur in enteroviral encephalitis.\textsuperscript{110}

For the treatment of HSV encephalitis in neonates, the recommended treatment\textsuperscript{104} is:

acyclovir 20 mg/kg IV, 8-hourly for 21 days
For the treatment of HSV encephalitis in older infants and children, we recommend:

acyclovir 10 mg/kg IV, 8-hourly for 14–21 days

### 10.8 Mycoplasma meningoencephalitis

*M. pneumoniae* is a respiratory pathogen that can cause multisystem disease, including the CNS. CNS manifestations include meningoencephalitis, transverse myelitis, stroke, and radiculopathy.\(^{110–113}\)

The clinical presentation was described in a review of 58 children with *M. pneumoniae* encephalitis, of whom 76% had prior flu-like or respiratory symptoms and 40% had pulmonary infiltrates.\(^{112}\) Only 57% made a full recovery. Minor to major neurologic sequelae persisted in 34% and 5 patients (9%) died. Poor outcome was associated with higher CSF white count and protein and older age.\(^{112}\)

Diagnosis is problematic. Serology is the mainstay, but the serum IgM level can remain elevated for many weeks after acute infection, and false-positive IgM tests are well recognized.\(^{110–113}\) PCR is more reliable on respiratory secretions than CSF: in one study, *M. pneumoniae* was diagnosed in 50 (31%) of 159 children with encephalitis, but CSF PCR was positive in only 11 of them.\(^{110}\) The diagnosis was confirmed by serology or throat swab PCR in the rest.

The pathogenesis of mycoplasma encephalitis is unknown and the optimum treatment unclear. Various therapies have been used, including antibiotics, corticosteroids, intravenous immunoglobulin (IVIG), and plasmapheresis, but none has been studied in an RCT\(^{110–113}\). There is little evidence of active infection in the brain, and some patients recover completely without antibiotics.\(^{110–113}\) The role of corticosteroids is uncertain. A recent case report described a 17-year-old whose neurologic symptoms resolved while receiving corticosteroid therapy, relapsed after they were stopped, and resolved again when they were restarted.\(^{114}\) A literature review found that 11 of 14 children (78%) treated with corticosteroids had a near or complete recovery.\(^{114}\) In a previous study, 56% of children not treated with corticosteroids recovered but the rest died or had severe neurologic sequelae.\(^{115}\) This sort of comparison with a historic control group provides only weak evidence for steroids.

### 10.9 Acute disseminated encephalomyelitis (ADEM)

ADEM was first described in the eighteenth century as a post-infectious encephalopathy, usually following measles, chicken pox, or smallpox.\(^{116}\) A paper published in 1931 described three forms of ADEM: post-infectious cases, cases occurring post-vaccination, and spontaneous cases with no apparent cause.\(^{117}\) The prognosis was poor for the post-infectious cases, but good for the rest.

Nowadays, ADEM is described as a monophasic, demyelinating disease of the CNS, which is rare (0.8 per 100,000 children per annum) and affects mainly young children and adolescents.\(^{118,119}\)

ADEM is thought to be a post-infectious phenomenon. In a review of ADEM, 50–75% of patients had fever and often respiratory symptoms in the preceding 4 weeks.\(^{118}\) An agent is identified in up to 75% of cases,\(^{118}\) although in one pediatric series only 1 of 18 children had a firm etiologic diagnosis.\(^{118}\) Cases have been described post-immunization (e.g., with measles or MMR vaccine), although at a far lower rate than with wild-type measles.\(^{116}\) A wide range of pathogens has been described in association with ADEM, including measles, rubella, varicella, influenza, EBV, CMV, coxsackievirus, HIV, HSV, group A streptococcus, *Mycoplasma, Bartonella henselae, Chlamydia*, and leptospirosis.\(^{118}\)

Two main pathogenetic mechanisms are postulated. The first is the inflammatory cascade concept in which direct CNS infection results in tissue damage and release of antigens into the systemic circulation, which elicits an immune response. The second is the molecular mimicry concept in which there is some degree of homology between the pathogen and the myelin proteins. A pathogen-initiated immune response can then, theoretically, be reactivated against “self” tissue.\(^{118}\)

The main clinical features of ADEM are fever, headaches, ataxia, and altered level of consciousness. Focal motor and sensory deficits are more common with increased age.\(^{118}\)

CSF pleocytosis is usual, although not invariable. Oligoclonal bands may be present. The most characteristic findings on MRI scan of the brain are multifocal white matter lesions, most clearly defined on T2-weighted and FLAIR images, and consistent with widespread CNS demyelination, although these
changes are non-specific.\textsuperscript{118} ADEM remains a diagnosis based on a poorly defined combination of clinical, laboratory, and radiologic criteria.\textsuperscript{118,119}

There are no trials of therapy in the management of ADEM. Intravenous corticosteroids (high-dose methylprednisolone) are the accepted first-line treatment, based on empirical observational studies and expert opinion.\textsuperscript{118–120} IVIG and plasmapheresis have been tried in individual cases with variable success.\textsuperscript{118–120} The current recommendations are for a 5–7-day course of intravenous corticosteroids followed by a prolonged course (3–6 weeks) of oral steroids.\textsuperscript{118,119}

The acute mortality of ADEM is 5–10%. Most patients who survive improve in a few months and 70–90% of patients suffer no residual neurologic symptoms at 18 months.\textsuperscript{118–120}

### 10.10 Lyme meningitis

Children with Lyme meningitis have a more prolonged presentation, on average, than children with viral meningitis, and are more likely to have cranial nerve signs including facial nerve palsy, papilledema, or erythema migrans.\textsuperscript{121–123}

The CSF in Lyme meningitis shows a lymphocyte or mononuclear cell predominance. In Lyme meningitis, the proportion of neutrophils is generally lower than in viral meningitis, and a CSF neutrophil count > 10% of the total CSF white count makes Lyme meningitis unlikely.\textsuperscript{121–123} The CSF protein is higher in Lyme meningitis than in viral meningitis: in one study\textsuperscript{122} the respective mean CSF protein was 1.1 and 0.4 g/L. Specific antibodies to \textit{Borrelia burgdorferi} can be demonstrated in the CSF in 25–92% of children with Lyme meningitis, but the sensitivity of PCR on CSF is only 5%.\textsuperscript{124}

An RCT of 21 patients with painful Lyme neuroborreliosis radiculitis and neuroborreliosis meningitis found no difference between 10 days’ treatment with either penicillin G or cefotaxime.\textsuperscript{125}

The American Academy of Pediatrics\textsuperscript{126,127} recommends treating Lyme meningitis for 30–60 days, but the Infectious Disease Society of America recommends 14–28 days.\textsuperscript{128} We could find no RCTs on duration of treatment, which should be individualized. We recommend:

- ceftriaxone 75–100 mg/kg (max 4 g) IV, daily
- OR cefotaxime 25 mg/kg (max 1 g) IV, 6-hourly
- OR benzylpenicillin 30 mg (50,000 U)/kg (max 1.2 g or 2 million U) IV, 4-hourly

### 10.11 Tuberculous meningitis (TBM)

**Clinical presentation of TBM**

TBM usually presents in an indolent fashion, over several days, with non-specific symptoms such as fever, anorexia, intermittent headache, or vomiting, and often with no definite neurologic manifestations. There may be intermittent drowsiness and even fluctuation in level of consciousness.\textsuperscript{127,128} TBM has traditionally been classified into three stages,\textsuperscript{129} and subsequent studies have shown that the staging has prognostic significance\textsuperscript{130}:

- **Stage I:** Non-specific symptoms such as fever, anorexia, intermittent headache, or vomiting, with no definite neurologic manifestations.
- **Stage II:** Drowsiness and disorientation and with signs of meningeal irritation and/or evidence of increased intracranial pressure.
- **Stage III:** Usually unconscious, with paralysis and signs indicating severe intracranial hypertension.

A study in Egypt compared 134 children with culture-proven TBM with 709 children with bacterial meningitis due to pyogenic bacteria.\textsuperscript{130} The clinical features that predicted TBM were headache and length of clinical history > 5 days.

A retrospective review of 214 children with TBM from Turkey reported a mean age of onset of 4.1 years, with most children (56%) in Stage II.\textsuperscript{131}

**Diagnosis of TBM**

The diagnosis of TBM is based on a combination of one or more of:

- clinical presentation;
- family history of TB;
- tuberculin skin test;
- chest radiographic changes;
- cerebral imaging;
- acid-fast bacilli in sputum or CSF;
- CSF changes: lymphocytosis, high CSF protein, low CSF glucose;
- PCR on CSF;
- culture of TB from CSF or sputum (takes weeks).
Each of the above has a variable incidence in different studies and none was reported to be present in all patients. In the Turkish study, a family history was found in 66%, 30% of children with TBM had a positive tuberculin skin test, and 87% had suggestive radiologic features of hilar adenopathy, miliary TB, infiltrates, or rarely (1%) pleural effusion.\textsuperscript{130} Cerebral imaging showed hydrocephalus in 80%, parenchymal cerebral changes in 26%, basal meningitis in 15%, and tuberculomas in 2%. Only 13% of children had acid-fast bacilli seen on Ziehl–Nielsen stain of CSF.\textsuperscript{130} In the Egyptian study, the patients with TBM were significantly more likely to have a CSF white cell count <1000 cells/mm\(^3\) (1000 \(\times\) 10\(^6\)cells/L), CSF lymphocyte count >30% of total, and CSF protein >100 mg/dL (1.0 g/L).\textsuperscript{131} A meta-analysis of commercially available nucleic acid amplification tests (PCR) on CSF for \textit{M. tuberculosis}\textsuperscript{132} found a sensitivity of only 56% and specificity of 98%. A positive PCR on CSF is, therefore, likely to be true, but a negative PCR certainly does not exclude TBM. Quantification of CSF interferon-gamma is under investigation.\textsuperscript{133}

**Treatment of TBM**

**Antituberculous drugs**

Because no combination of the above tests is sufficiently sensitive to be able to confidently exclude TBM and because of the poor prognosis if treatment is delayed, it is not unusual to commence empiric antituberculous therapy on suspicion. If so, the evidence for continuing therapy should be reevaluated regularly.

There is only one RCT of antituberculous antimicrobials in children with TBM, who received isoniazid plus streptomycin plus either rifampin (36 patients) or ethambutol (35 patients).\textsuperscript{134} There was no difference in outcome. Streptomycin is rarely used nowadays because it has to be given by IM injection and is toxic. Current recommendations are usually for four antituberculous antimicrobials, but there is no evidence that this is superior to using three.

For the daily regimen, we recommend:

- **isoniazid 10 mg/kg (max 300 mg) orally, daily for 12 months PLUS**
- **rifampicin 10 mg/kg (max 600 mg) orally, daily for 12 months PLUS**

\* **ethambutol 15 mg/kg (child \(\geq 6\) years) orally, daily for 2 months PLUS**

**pyrazinamide 25 mg/kg (max 2 g) orally, daily for 2 months**

For the three-times-weekly regimen, we recommend:

- **isoniazid 15 mg/kg (max 600 mg) orally, three times weekly for 12 months PLUS**
- **rifampicin 15 mg/kg (max 600 mg) orally, three times weekly for 12 months PLUS**
- **ethambutol 30 mg/kg (child \(\geq 6\) years) orally, three times weekly for 2 months PLUS**
- **pyrazinamide 50 mg/kg (max 3 g) orally, three times weekly for 2 months**

\*Ethambutol should not be used in young children <6 years old, due to difficulties in assessing optic neuritis. For children <6 years old, we recommend using isoniazid, rifampicin, and pyrazinamide.]

We recommend discontinuing ethambutol once the organism is known to be sensitive to isoniazid and rifampicin, even if this is prior to 2 months; but continuing ethambutol if susceptibility results are not available at 2 months.

[NB: Because of the risk of isoniazid-induced pyridoxine deficiency, it is recommended to give pyridoxine 5 mg orally to breast-fed babies with each dose of isoniazid (you may need to crush a 25 mg tablet, dissolve in 5 mL of water, and give 1 mL).]

**Corticosteroids in TBM**

Corticosteroid adjunctive therapy improves outcome in TBM.\textsuperscript{135–137} One placebo-controlled RCT of prednisolone 2–4 mg/kg/day for 1 month in children with TBM showed corticosteroids improved mortality and intellectual outcome,\textsuperscript{135} and this and another RCT\textsuperscript{136} both showed that steroid-treated children had more rapid resolution of tuberculomas. Both studies used 4 mg/kg of prednisolone instead of the usual dose of 2 mg/kg for theoretical reasons.

A Cochrane meta-analysis of corticosteroids for TBM showed benefit, but was unable to comment on dose of corticosteroids or to separate adults from children.\textsuperscript{137}

In a large placebo-controlled RCT in 545 adults and adolescents with TBM, treatment with dexamethasone was associated with a reduced risk of death (RR 0.69, 95% CI 0.52–0.92), but not with improved
morbidity.\textsuperscript{138} The dexamethasone regime was a complicated one, not easily extrapolated to children.

We do not feel that the evidence justifies using 4 mg/kg of prednisolone rather than the usual 2 mg/kg. We recommend adjunctive therapy, using:

**prednisolone 2 mg/kg (max 80 mg) orally, daily for at least 4 weeks**

**Thalidomide in TBM**

There has been interest in the use of thalidomide as adjunctive therapy in TBM, because of its anti-inflammatory action. An RCT of high-dose thalidomide in children with TBM was terminated early because of a high incidence of adverse events, and possibly increased mortality in the treatment group.\textsuperscript{139} Thalidomide is not recommended.

### 10.12 Cryptococcal meningitis

Cryptococcal meningitis, previously known as torulosis, is caused either by *Cryptococcus neoformans* (particularly in immunocompromised patients, such as HIV infection) or *C. gattii* (previously known as *C. neoformans* var. *gattii*). The diagnosis is made by seeing encapsulated yeast cells on Indian ink or other stain of CSF and by growing the yeast. The management of children with cryptococcal meningitis is complicated and we strongly recommend a pediatric infectious disease consultation.

Because of its rarity, there are no studies of antifungal therapy of immunocompetent patients. Studies of HIV patients have shown that combination therapy with amphotericin B plus flucytosine is superior to amphotericin B alone,\textsuperscript{140,141} or to amphotericin B plus fluconazole,\textsuperscript{141} or to amphotericin B plus flucytosine plus fluconazole.\textsuperscript{141} Liposomal amphotericin sterilizes the CSF more quickly than amphotericin B alone and is less nephrotoxic, but does not improve prognosis and is far more expensive.\textsuperscript{142}

The standard recommended treatment\textsuperscript{140,141} for cryptococcal meningitis is:

amphotericin B desoxycholate 0.7 mg/kg IV, daily for 6–10 weeks PLUS flucytosine 25 mg/kg IV or orally, 6-hourly for 6–10 weeks

If amphotericin B causes unacceptable renal or systemic toxicity, liposomal amphotericin B 4 mg/kg IV daily should be used.\textsuperscript{142} Patients infected with *C. gattii* may respond slowly and require longer treatment. Alternatively, if the CSF is culture negative after 2 weeks of therapy, it would be reasonable to stop the amphotericin B desoxycholate and flucytosine and commence:

flucytosine 12 mg/kg (max 800 mg) orally or IV for the first dose, then 6 mg/kg (max 400 mg) orally, daily for at least 10 weeks

Itraconazole has been successfully used when fluconazole cannot be used.

In HIV-infected patients, the above regimen has been shown to be successful, without the need for culture negativity at 2 weeks.

Long-term suppressive therapy may be required for immunocompromised patients. If the patient has responded well to 10 weeks of fluconazole at the above dose, secondary prophylaxis is recommended at a reduced dose:

flucytosine 3 mg/kg (max 200 mg) orally, daily, continued while immunosuppressed

### 10.13 Transverse myelitis

Acute transverse myelitis (ATM) is a rare disease in childhood and adolescence, with an incidence of 1–4 per million new cases annually, and peaks at 10–19 years and 30–39 years.\textsuperscript{143} Transverse myelitis is due to inflammation of the spinal cord, usually secondary to infection with enteroviruses,\textsuperscript{144} arboviruses, other viruses or *M. pneumoniae*.\textsuperscript{145} It has been described in many conditions, including Lyme disease\textsuperscript{146} and in cysticercosis. It has occasionally been described in association with immunization with various live and inert vaccines including influenza, MMR, and oral polio vaccines,\textsuperscript{147,148} although there is insuf- ficient evidence to say whether immunizations can cause transverse myelitis or whether paralysis from another cause merely occurs coincidentally following immunization.\textsuperscript{149}

The clinical presentation of transverse myelitis is characterized by paraplegia, with or without sensory symptoms, and bladder dysfunction. It typically manifests itself over a period of hours to 1 week. The major differential diagnosis is a pyogenic epidural abscess, which requires urgent drainage (see Section 10.4, p. 143). For this reason, radiologic investigation with
MRI or CT scan is a priority. An expert working group has proposed diagnostic criteria.\textsuperscript{143}

We found no trials of the use of corticosteroids in ATM, which is hardly surprising given its rarity. A retrospective review of 50 Japanese children with ATM found that younger children and those with neurologic features of paraplegia did worse, and that corticosteroid therapy did not appear to improve outcome.\textsuperscript{150} Intravenous corticosteroids (high-dose methylprednisolone as for ADEM; see Section 10.9, p. 146) are often used empirically. ATM often leads to long-term bladder and/or bowel dysfunction.\textsuperscript{151}

### 10.14 Guillain–Barré Syndrome

Guillain–Barré syndrome is an acute peripheral neuropathy which causes ascending paralysis due to multifocal inflammation of the spinal roots and peripheral nerves, especially their myelin sheaths. In severe cases the axons are also damaged.\textsuperscript{152} In the commonest form of GBS in Europe and North America, the underlying pathologic process is an acute inflammatory demyelinating polyradiculoneuropathy.

In all series, about two-thirds of patients have had an infection within the previous 6 weeks, most commonly a flu-like illness but also gastroenteritis. About a quarter of patients with Guillain–Barré syndrome have had a recent \textit{Campylobacter jejuni} infection, and they are particularly likely to have an axonal neuropathy.\textsuperscript{152} Observational and case-control studies implicate a range of bacteria (including \textit{M. pneumoniae}) and viruses such as EBV and CMV as possible triggers for the syndrome. There is also an association with immunization with rabies vaccine\textsuperscript{153} (incidence 1 in 1000 doses) and previously but not currently with inactivated influenza vaccine in the USA\textsuperscript{154} (1 in 1,000,000 doses).

The pathogenesis is thought to be an autoimmune response directed against antigens in the peripheral nerves that is triggered by a preceding infection. Antibodies or T cells stimulated by antigens on the infecting microbe may cross-react with neural antigens.\textsuperscript{152} Guillain–Barré causes the development of weakness and usually numbness of the limbs and often the facial, swallowing, and breathing muscles. The weakness reaches its nadir within a few days or up to 4 weeks. In 25% of patients it is sufficiently severe to require the use of artificial ventilation, and 3.5–12% of patients die of complications.\textsuperscript{152} Recovery takes several weeks or months.

The diagnosis is made clinically and confirmed by neurophysiologic studies.\textsuperscript{152} CSF protein is raised in about 80% of cases and there are no white cells in the CSF (the presence of CSF pleocytosis indicates another diagnosis).\textsuperscript{152} A Cochrane review found six studies (649 patients) that compared plasma exchange with supportive therapy and found that plasma exchange hastened motor recovery.\textsuperscript{155} A separate Cochrane review compared IVIG with plasma exchange.\textsuperscript{156} There were five eligible RCTs (536 patients). In severe disease, IVIG started within 2 weeks from onset hastened recovery as much as plasma exchange, and was significantly more likely to be completed than plasma exchange. Giving IVIG after plasma exchange did not confer significant extra benefit. There was only one study exclusively in children which found that a total dose of 2 g/kg of IVIG hastened recovery compared with supportive care alone, whether it was given in divided doses over 2 or 5 days.\textsuperscript{157}

A Cochrane review of six trials (587 participants) of corticosteroids found limited evidence that oral corticosteroids significantly slow recovery from Guillain–Barré syndrome.\textsuperscript{158} Intravenous methylprednisolone alone was not found to produce significant benefit or harm.

We recommend:

\[\text{IVIG 1 g/kg, infused IV over 8–12 hours, once daily for 2 days}\]

### 10.15 PANDAS

Pediatric autoimmune neuropsychiatric disorders or PANDAS is a group of disorders which some have suggested are associated with streptococcal infections, possibly analogous to Sydenham's chorea. Patients have prepubertal onset of obsessive-compulsive disorder and tic disorders, and exacerbations may be associated with group A beta-hemolytic streptococcal (GBS) infections. In one descriptive study of 50 children, the clinical course was characterized by a relapsing–remitting symptom pattern with significant psychiatric comorbidity accompanying the exacerbations of emotional lability, separation anxiety, nighttime fears, bedtime rituals, cognitive deficits,
oppositional behavior, and hyperactivity. Symptom onset was reported to be triggered by proven or possible group A streptococcal infection in about 70% of episodes.\textsuperscript{159}

There is doubt whether the condition is a real entity. In a controlled study of unselected patients with Tourette syndrome and/or obsessive-compulsive disorder, there was no clear relationship between new GABHS infections and symptom exacerbations.\textsuperscript{160} We could find only two controlled treatment studies. In one placebo-controlled study, penicillin prophylaxis did not reduce the number of exacerbations of PANDAS, but nor did it reduce the number of infections.\textsuperscript{161} Another study found that children on either penicillin or azithromycin had fewer infections and fewer exacerbations than the previous year, but the results are not helpful as the study did not include a placebo group.\textsuperscript{162}

References

31 Berg B, Gardsell P, Skansberg P. Cerebrospinal fluid lactate in the diagnosis of meningitis: diagnostic value compared
55 Lin TY, Chrane SF, Nelson JD et al. Seven days of ceftriaxone therapy is as effective as ten days’ treatment for bacterial meningitis. JAMA 1985;253:3539–63.
The Cochrane Database of Systematic Reviews 2006;(1): Art No CD004884.


 Hannoverschen Cochlear Implant-Gesellschaft e.V. Meeting on post cochlear implantation meningitis. Schiphol Airport, Amsterdam, the Netherlands, July 5, 2002 [Minutes; German]. Available at http://www.hcg.de.


Tyler KL. Herpes simplex virus infections of the central nervous system: encephalitis and meningitis, including Molaret’s. Herpes 2004;4(11(supp 2)):75A–64A.


Nigrovic LE, Kuppermann N, Malley R. Development and validation of a multivariable predictive model to distinguish
bacterial from asceptic meningitis in children in the post-


104 Kimberly D. Herpes simplex virus meningitis and encephalitis in neonates. *Herpes* 2004;11(suppl 2):65A–76A.


CHAPTER 11
Osteomyelitis and septic arthritis

11.1 Acute osteomyelitis

Acute osteomyelitis is rare in infants and children, with an annual incidence in children of 1 in 5,000 to 1 in 10,000 per annum.1–4 Infection is usually hematogenous, although organisms can be introduced by trauma or iatrogenically or can spread from contiguous structures such as joints. About a third of children with acute osteomyelitis give a history of recent minor trauma,1–4 but such a history would probably be equally common in young children without osteomyelitis.

Boys are twice as likely to be affected as girls and half of the children are <5 years old. Infection of the long bones (femur, tibia, humerus) is more common in children than infection elsewhere, such as the spine or pelvis, whereas involvement of the axial skeleton is more likely in adults.1–4 A single site of infection is most common, but 5–20% of children have multifocal pyogenic osteomyelitis.1–4

Diagnosis of acute osteomyelitis

Osteomyelitis can be misdiagnosed as cellulitis, which also presents with fever, tenderness, and swelling. Conditions that can mimic osteomyelitis include fractures and tumors.

Clinical features of acute osteomyelitis

The cardinal clinical features of acute osteomyelitis in children are fever, pain, limitation of movement of the limb, and exquisite sensitivity to local pressure (“point tenderness”).1–3 This is because an abscess forms under the periosteum. In a series of 100 children with extremity pain, 61 had bone scans suggestive of osteomyelitis.5 Although usually acute, infection can sometimes be indolent.

In newborns and young infants, the periosteum is thin and pus can rupture through into the soft tissues, so they tend to present with local swelling, resembling cellulitis, or skin abscess, but with less local tenderness.6,7 In addition, babies are more likely to have septic arthritis as well as osteomyelitis, probably because pus ruptures from the bone into the joint.6,7

Laboratory tests in acute osteomyelitis

The ESR and acute phase reactants such as CRP (C-reactive protein) are raised in at least 90% of children with acute osteomyelitis.1–4 Normal values make osteomyelitis less likely but do not exclude it, while raised values are non-specific. The peripheral blood white cell count is often normal and is less useful than ESR and CRP.1–4

Blood cultures may be positive in up to 60% of patients,8 although the proportion with positive blood cultures is usually much lower.1–4 The diagnostic yield can be increased substantially, to 50–80%, by using needle aspiration or surgical biopsy to obtain bone, soft tissue, or joint fluid. The needle aspiration can be ultrasound guided to improve the yield in difficult cases.9

Imaging in acute osteomyelitis

Plain radiographs are of little use in the early diagnosis of pediatric osteomyelitis, except occasionally in neonatal osteomyelitis. In older children, the X-ray may show non-specific soft-tissue swelling in the first 3 days, but typical changes of osteopenia or osteolysis do not appear until after 7 days, periosteal elevation from 10 to 20 days, and osteosclerosis not before 30 days.10

Ultrasound scans can be useful in localizing collections such as sub-periosteal abscesses, in distinguishing infection from other diagnoses, and in directing fine needle aspiration.9 Ultrasound is non-invasive, cheap, and less subject to movement artifact than magnetic resonance imaging (MRI) or computed tomography.

The antibiotics and doses recommended in this chapter are based on those in Therapeutic Guidelines: Antibiotic, 13th edn, Therapeutic Guidelines Ltd, Melbourne, 2006.
(CT) (so does not require a general anesthetic in young children). In a prospective study of imaging of 65 children with suspected osteomyelitis, ultrasound influenced treatment in 30% of cases, second only to MRI (45%) and better than CT scan.

**Bone scan in acute osteomyelitis**
The technetium radionuclide bone scan involves IV injection of radioactive technetium-99m (99mTc). This is carried in the bloodstream to areas of maximum perfusion, so a scan within an hour of injection will show increased uptake (a “hot spot”) in areas of hyperemia including both cellulitis and osteomyelitis. After a few hours, however, the 99mTc is preferentially taken up by osteoblasts. Delayed bone scans will, therefore, show increased uptake in areas of increased new bone formation. Technetium bone scan has a sensitivity of 80–100% in diagnosing acute osteomyelitis in children of all ages, including neonates. The main diagnostic pitfalls are that the bone scan may be normal early in the infection and that the scan may show areas of decreased uptake of isotope due to impaired bone perfusion causing bony necrosis in children with more aggressive osteomyelitis.

Nuclear medicine is particularly useful in identifying multifocal pyogenic osteomyelitis, which is more common in children than adults. In this case, bone scan may demonstrate multiple “hot spots,” which may or may not be associated with signs or symptoms. Multifocal pyogenic osteomyelitis is different from chronic multifocal osteomyelitis, which is non-infective (see Section 11.4, p. 160).

**Other radionuclide scans**
Gallium scanning using the radioactive isotope 67Ga depends on gallium being taken up preferentially by iron-metabolizing cells, including neutrophils. It is most useful in spinal osteomyelitis. Intense uptake of gallium in two adjacent vertebrae with loss of the disc space is highly suggestive of spinal osteomyelitis.

Indium-labeled white cell scanning using 111In is no more accurate than 99mTc scanning, takes longer and is more difficult, and is rarely necessary in pediatric osteomyelitis.

**MRI and CT scans in acute osteomyelitis**
MRI with enhancement has a sensitivity of 88–100% for diagnosing acute osteomyelitis, can reveal subperiosteal and epiphyseal involvement not seen otherwise, and is more sensitive than CT. Although the specificity is usually quoted as >90%, MRI scans may incorrectly identify healing fractures, infarcted bone and healing infection as acute osteomyelitis, and are not usually necessary in uncomplicated cases.

CT scans are most useful for guided interventional procedures (e.g., aspiration or drainage) and for evaluation of sinus tracts in chronic infections.

**Organisms in acute osteomyelitis**
*Staphylococcus aureus* causes >80% of childhood osteomyelitis, including developing countries. To date, MRSA osteomyelitis, either community-acquired (cMRSA) or nosocomially acquired, is responsible for 10% of cases in most countries worldwide, although there may be regional variation. In the USA, in contrast, cMRSA is responsible for an increasing proportion of cases, over 50% in recent series.

Other organisms are relatively uncommon causes of acute osteomyelitis, but should be strongly considered in certain settings:
- Group B streptococcus is an important cause of neonatal osteomyelitis, and MRSA should also be considered.
- *Streptococcus pneumoniae* and *Salmonella* are important causes in sickle cell disease.
- *Kingella kingae* is increasingly recognized as a cause of osteoarticular infections in children <5 years old.
- Penetrating injuries to the sole of the foot ("sneaker osteomyelitis") are strongly associated with *Pseudomonas* infection.
- *Haemophilus influenzae* type b (Hib), which was an important cause of osteoarticular infections in children <5 years old, is scarcely reported in well-immunized populations, but should be considered in unimmunized children.
- *Bartonella henselae* (cat scratch) can cause acute or chronic vertebral osteomyelitis.
- Children with chronic granulomatous disease are susceptible to fungal osteomyelitis, particularly with *Aspergillus*, as of course are highly immunocompromised children.

Other organisms that can cause osteomyelitis include group A streptococcus (often in association with chicken pox), anaerobes, *Salmonella* (in association...
with food poisoning), other Gram-negative organisms (in developing countries and in association with surgery), and coagulate negative staphylococci (virtually always in association with surgery).

**Antibiotic therapy of acute osteomyelitis**

Treatment should be based on cultures from bone, soft tissue, joint fluid, and of course blood cultures, whenever possible. We could find only 1 RCT comparing different antibiotics for acute pediatric osteomyelitis (we excluded 1 RCT that had only nine children with osteomyelitis). This small study, before cMRSA was reported, found no difference between IV clindamycin and IV methicillin or nafcillin. We found observational studies indicating that several different regimens were effective. We found a non-Cochrane systematic review that found no difference in outcome of acute osteomyelitis between beta-lactam and macrolide antibiotics, although only 1 of 12 studies included was an RCT.

**Antibiotic therapy of acute osteomyelitis**

For **empiric therapy**, in the absence of any other indications, we recommend:

- di/flucl/oxa/nafcillin 50 mg/kg (max 2 g) IV, 6-hourly OR
- cephalothin 50 mg/kg (max 2 g) IV, 6-hourly OR
- cephazolin 50 mg/kg (max 2 g) IV, 8-hourly

followed as soon as possible (see p. 159) by:

- di/flucloxacin 25 mg/kg (max 1 g) orally, 6-hourly OR
- cephalaxin 25 mg/kg (max 1 g) orally, 8-hourly

When cMRSA infection is suspected, because of local prevalence and/or ethnicity, or clindamycin-sensitive cMRSA is grown, we recommend:

- clindamycin 10 mg/kg (max 450 mg) IV, 8-hourly THEN (if susceptible)
- clindamycin 10 mg/kg (max 450 mg) orally, 8-hourly

Clindamycin is rapidly and almost completely absorbed after oral administration, and is effective. We recommend to change to oral therapy once the patient is responding to IV treatment.

For patients with anaphylactic penicillin allergy, we recommend:

- vancomycin <12 years: 30 mg/kg (max 1 g) IV, 12-hourly; 12 years and older: 25 mg/kg (max 1 g) IV, 12-hourly OR
- clindamycin 10 mg/kg (max 450 mg) IV, 8-hourly THEN (if susceptible)
- clindamycin 10 mg/kg (max 450 mg) orally, 8-hourly

If *S. aureus* is grown and is resistant to macrolides, and the patient is allergic to penicillin, we recommend basing oral therapy following vancomycin on proven susceptibility. Suitable oral options may be trimethoprim-sulfamethoxazole or doxycycline.

For patients with probable or proven hospital-acquired MRSA, we recommend:

- vancomycin <12 years: 30 mg/kg (max 1 g) IV, 12-hourly; 12 years and older: 25 mg/kg (max 1 g) IV, 12-hourly THEN (if susceptible)
- rifamp(inc)in 10 mg/kg (max 600 mg) orally, daily PLUS EITHER
- fusidate sodium tablets 12 mg/kg (max 500 mg) orally, 12-hourly OR
- fusidic acid suspension 18 mg/kg (max 750 mg) orally, 12-hourly

If Gram-negative infection (other than *Pseudomonas*) is suspected, and for children <5 years not immunized against Hib, we recommend:

- cefotaxime 50 mg/kg (max 2 g) IV, 8-hourly OR THE COMBINATION OF
- ceftriaxone 50 mg/kg (max 2 g) IV, daily PLUS di/flucl/oxa/nafcillin 50 mg/kg (max 2 g) IV, 6-hourly
- THEN (if susceptible)
- amoxicillin+clavulanate 22.5 + 3.2 mg/kg (max 875 + 125 mg) orally, 8-hourly

For suspected *Pseudomonas* osteomyelitis (penetrating wound to foot through sneaker), we recommend:

- cefazidime 50 mg/kg (max 2 g) IV, 8-hourly OR
- ciprofloxacin 10 mg/kg (max 400 mg) IV, 12-hourly OR
- piperacillin 100 mg/kg (max 4 g) IV, 8-hourly OR
- ticarcillin 50 mg/kg (max 3 g) IV, 6-hourly

We recommend changing antibiotics if indicated by culture and sensitivity results. If the clinical response is
good and the culture results are negative or if sensitive
S. aureus is cultured, continue with the appropriate
regimen mentioned above.

Antibiotics for acute osteomyelitis due to other
organisms
For directed therapy of osteomyelitis due to other or-
organisms, we recommend advice from an infectious
diseases physician or clinical microbiologist. We rec-
ommend not using aminoglycosides for longer than a
week, because of the risk of cumulative toxicity (see
Appendix 2)

Mode of delivery of antibiotics for acute
osteomyelitis

**Question** | For children with osteomyelitis, does
changing from parenteral to oral antibiotics after less
than a week compared with longer parenteral therapy
result in increased morbidity?

**Literature review** | We found 1 RCT, 12 observational
studies, and a non-Cochrane systematic review of
antibiotic duration.46 We found 1 observational study on
adverse effects of prolonged IV therapy.46

A systematic review compared the outcome at 6 months
in children aged 3 months to 16 years with acute
osteomyelitis treated with 3–6 days of IV antibiotics
followed by oral antibiotics, and in children treated
with 7 or more days of IV antibiotics followed by oral
antibiotics.46 Most of the cases were due to S. aureus.
The overall cure rate at 6 months for the short course
of IV therapy was not significantly different from the
longer course: 95.2% (95% CI 90.4–97.7) and 98.8% (95% CI 93.6–99.8), respectively.46

Prolonged IV therapy is not without risks. An observ-
ational study reported that 41% of 75 children given
IV antibiotics by central venous catheter had one or
more catheter-associated complication.48

To treat acute osteomyelitis in children 3 months
or older, we recommend changing from IV
antibiotics to oral antibiotics after 3–6 days if the
child is afebrile and improving clinically.
To treat newborns and infants <3 months old,
whose absorption and intake of oral medications
is unreliable, therapy should be given
intravenously for the entire duration.

Duration of antibiotics for acute osteomyelitis
We could find no RCTs on overall duration of antibi-
totics for acute osteomyelitis. A systematic review of
short-course IV therapy46 identified two old studies,
each including over 100 children, in which antibiotics
were given for <3 weeks, and the success rates were only
82 and 81%.149 For this reason, it is recommended to
treat with a total of at least 3 weeks of antibiotics (IV
plus oral). There is, however, wide variation between
studies regarding failure rates according to treatment
duration. A series of smaller studies quoting 1–52 days
of parenteral antimicrobial therapy reported success
rates from 81 to 100%.46 There is no evidence that giv-
ing antibiotics for longer than 3 weeks improves the
success rate.

Serum CRP levels falls quicker than ESR in children
recovering from acute osteomyelitis. Studies that mea-
sured serial CRP and ESR found that children with
raised CRP levels were more likely to have symptoms
or extensive radiographic abnormalities.50,51 This does
not mean that a raised CRP after 3 weeks of antibiotics
would be an indication to continue treatment if the
child was asymptomatic, but it might be an indication
to examine the child carefully and to perform imaging.

We recommend treating children with acute
osteomyelitis with antibiotics for a total of at
least 3 weeks.

11.2 Acute diskitis (discitis)
Childhood diskitis is probably a continuum of spinal
infections, from infection of the intervertebral disk
alone to vertebral osteomyelitis with soft-tissue abscess.
It has been recognized for decades in the pediatric pop-
ulation, with controversy about the etiology and opti-
mal treatment.52–54 Diskitis is now generally accepted
as a bacterial infection involving the disk space and
adjacent vertebral end plates.52,53

Childhood diskitis can occur in the thoracic, lumbar,
or sacral spine and can affect children of all ages, but
lumbar diskitis in children <5 years is commonest.52–54
The presentation of diskitis varies with age. Classically,
the child refuses to walk, crawl, or stand, and may have
back pain or pain on changing diapers. Nighttime cry-
ing can be a feature in toddlers,54 and limp with irrit-
ability in older children. Fever is often low grade or
absent, and acute phase reactants are less likely to be
elevated than in acute osteomyelitis.53,54
CT-guided biopsy yields an organism in only 37–60% of cases, probably due to confounding factors such as low numbers of organisms, previous antibiotics and technique, rather than absence of infection. This yield is compatible with biopsy results in pediatric acute osteomyelitis and septic arthritis. Biopsy is not considered necessary for children with a classic clinical presentation, but is indicated for those whose symptoms do not resolve rapidly with treatment or who have an atypical presentation. The diagnosis is usually made clinically and confirmed by changes in the plain radiograph, bone scan, or MRI scan. Blood cultures may be positive.

The most common organism identified is *S. aureus*, but other organisms including *Salmonella*, *K. kingae*, and anaerobes have been described.

Most children improve rapidly with antibiotics. We recommend using the same antibiotics as for acute osteomyelitis (see p. 158). There are no RCTs for treatment of diskitis, and the optimum duration of therapy is unknown. Pain often persists and the course can be indolent. There is no evidence and little reason to continue IV antibiotics once the child is afebrile and mobile, usually after about a week. A recent review suggested that oral antibiotics should be continued for about 4–6 weeks, depending on resolution of symptoms. Diskitis often behaves more like chronic than acute osteomyelitis, so extending the duration of oral antibiotics seems reasonable.

Rest and immobilization with a lumbar sacral corset or thoracolumbosacral orthosis are sometimes recommended in conjunction with antibiotics, particularly if imaging studies show sagittal or coronal deformity of the spine, or extensive bony destruction and soft-tissue involvement.

Young children do not like rest, corsets, and orthoses, and there is no good evidence that they improve outcome. Children generally recover without them.

There is little value in repeating radiographs or MRI scans frequently in follow-up, because these are slow to resolve and do not equate with cure. Imaging is necessary only if there are problems, and possibly at 12–18 months to show regrowth of the disk space. The duration of oral antibiotics can be determined by clinical response, and the return of acute phase reactants to normal may be useful in this setting.

### 11.3 Chronic osteomyelitis

Chronic osteomyelitis has been defined as bone infection requiring more than one episode of treatment and/or a persistent infection lasting more than 6 weeks. The diagnosis is usually made clinically and confirmed by plain X-ray and/or scan followed by biopsy. A systematic review of diagnostic techniques in chronic osteomyelitis occurring at all ages, including cases associated with metal implants, found that positron emission tomography was most sensitive (96%), compared with MRI (84%) and bone scan (82%).

In chronic infections, sinus cultures are often misleading, because the sinus tract becomes secondarily infected with water-loving Gram-negative bacilli. Deep bone biopsy is recommended, whenever possible, although may be negative because of prior antibiotics and low organism load. Chronic osteomyelitis or arthritis associated with prosthetic material rarely recovers unless the prosthetic material is removed. Chronic osteomyelitis of the mandible should rouse suspicion of actinomycosis.

There is no evidence for or against the practice of using probenecid to increase antibiotic levels, but probenecid is often poorly tolerated and so may impair compliance. Nor is there evidence about the use of antibiotic-impregnated beads in chronic infection, usually containing gentamicin, but more recently ceftriaxone, although there are concerns that this could induce antibiotic resistance.

We found no good studies, not even observational ones, on duration of treatment for chronic infectious osteomyelitis. Most authorities recommend at least 6 months of oral antibiotics, but the duration of IV therapy is unknown, and even whether IV antibiotics are needed at all, provided adequate bone levels can be achieved with oral therapy. Unless there is evidence to suggest otherwise, we recommend that the antibiotic regimen includes an antibiotic against *S. aureus*.

### 11.4 Chronic recurrent multifocal osteomyelitis

Chronic recurrent multifocal osteomyelitis (CRMO) is a rare condition characterized by multifocal recurrent lesions with no infectious agents detectable in the bone
The lesions are often lytic. The lesion is a sterile inflammation of bone, of unknown etiology, although it has been postulated that patients may have a spondyloarthropathy.\textsuperscript{67,68}

CRMO is thought to be a non-infective condition, distinct from acute multifocal osteomyelitis caused by \textit{S. aureus} and other pyogenic organisms, and distinct from chronic pyogenic osteomyelitis (see Section 11.3, p. 160).

Some patients can present with a single non-infectious lesion that recurs in the same site, with the same clinical, radiological, and histological features as CRMO. This condition, sometimes called chronic recurrent unifocal osteomyelitis, is probably the same disease as CRMO.\textsuperscript{67,68}

CRMO can be associated with SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome,\textsuperscript{69} although few patients presenting with CRMO have all the features of the syndrome.\textsuperscript{67,68} If CRMO is suspected, the patient should be asked about and examined for palmar or plantar pustulosis, for psoriasis, and for joint involvement (including sacroiliac joints). Enthesitis (inflammation at the point of attachment of skeletal muscles to bone) may be present or may develop later.\textsuperscript{68} Inflammatory bowel disease is also described in association with CRMO.\textsuperscript{67,68}

CRMO mimics bacterial osteomyelitis clinically and histologically, and the diagnosis at first presentation is almost inevitably acute or chronic osteomyelitis. The recurrence of lesions despite adequate antibiotic treatment should alert the clinician to a possible diagnosis of CRMO. The median time to diagnosis was 8 months in one study.\textsuperscript{68}

The condition is too rare for RCTs of treatment, but the consensus view is that non-steroidal anti-inflammatory drugs relieve symptoms, while antibiotics make no difference.\textsuperscript{68}

### 11.5 Septic arthritis

Septic arthritis can occur as a result of hematogenous spread of organisms, with or without accompanying osteomyelitis, as a result of contiguous spread from osteomyelitis (e.g., in neonates, when pus is more likely to rupture through the periosteum) or following penetrating trauma. Arthritis may be monoarticular or occasionally polyarticular.

The major pathogen worldwide is \textit{S. aureus}, and cMRSA is being reported from the USA,\textsuperscript{69} Europe,\textsuperscript{70} Taiwan,\textsuperscript{71} and Australia.\textsuperscript{72} The organisms causing septic arthritis are similar to those causing osteomyelitis (see p. 157), and include \textit{S. pneumoniae}, group A (and in neonates, group B) streptococcus, \textit{K. kingae}, and \textit{Salmonella} species.\textsuperscript{69–72} In unimmunized populations, Hib is a major cause. There are, however, some organisms that are sometimes isolated from joints but virtually never from bone. These include \textit{Neisseria meningitidis}, \textit{N. gonorrhoeae}, and \textit{Enterobacter} species.\textsuperscript{69–72}

Children with septic arthritis present with pain, swelling, redness, and reluctance to move the joint. The diagnosis is primarily clinical,\textsuperscript{73} although a high fever (>38.5°C orally) and a high serum CRP\textsuperscript{74} can help distinguish septic arthritis of the hip from irritable hip.\textsuperscript{75} Diagnostic specimens, including a joint aspirate and blood cultures, should be taken before starting therapy, although the yield from Gram stain in one study\textsuperscript{76} was only 45%. The yield from synovial fluid culture is also lower, at 38–58%, than for bone cultures, presumably due to the antibacterial properties of synovial fluid.\textsuperscript{70–73} Because there may be minimal osteoblastic activity in septic arthritis, bone scan is less sensitive diagnostically than for osteomyelitis. Ultrasound can be useful in determining whether or not there is an effusion in a swollen joint and in aiding percutaneous drainage.

Drainage of infected joints is important for therapeutic as well as diagnostic reasons. Pus in the joint can cause permanent damage and impairs the action of antibiotics. Drainage may be achieved percutaneously, but open or arthroscopic surgery, often leaving a drain in situ, is usually needed for adequate drainage. Inflammation sometimes settles initially but recurs. This is an indication that further exploration and drainage is needed.\textsuperscript{70–73}

If possible, antibiotic therapy should be based on Gram stain of joint fluid. If not, empiric therapy should be as for osteomyelitis (see p. 158).

Gonococcal arthritis should be treated with cefotaxime or ceftriaxone until susceptibility tests are known. Treatment should continue for a total of 7 days. Joint washouts are usually unnecessary.

Tuberculous arthritis usually presents with a chronic monoarthritis, with no fever, and little or no
inflammation. If tuberculous arthritis is suspected or proven, see p. 201 for treatment.

The optimal duration of antibiotic therapy is unknown, but in line with treatment of osteomyelitis, we recommend IV therapy until there is an initial sustained clinical response (usually 3–7 days) followed by oral antibiotics to a total of at least 3 weeks, depending on clinical response.

A placebo-controlled RCT examined the use of 4 days of IV dexamethasone in 123 children with acute septic arthritis.\(^77\) Dexamethasone significantly shortened the duration of symptoms during the acute phase and reduced residual dysfunction at the end of therapy, after 6 months and after 12 months. We recommend, for proven acute septic arthritis, in addition to antibiotics:

\[
\text{dexamethasone } 0.2 \text{ mg/kg/dose IV, 8-hourly for 4 days}
\]

An evaluation of the implementation of clinical guidelines for the management of possible septic arthritis of the hip in children showed excellent results compared to historic controls.\(^78\) The patients treated using the guideline were more likely to have CRP measured before and after treatment, and had a significantly lower rate of initial bone scanning (13% versus 40%) and of presumptive drainage (13% versus 47%), greater compliance with recommended antibiotic therapy (93% versus 7%), faster change to oral antibiotics (3.9 days versus 6.9 days), and shorter hospital stay (4.8 days versus 8.3 days).\(^78\) Because there are great advantages to all in reducing the time on IV antibiotics, we recommend the application of evidence-based guidelines for treating septic arthritis and osteomyelitis.

### 11.6 Arthritis associated with other infections

Arthritis can be associated with many different infections. Infections include viral arthritis, e.g., rubella or parvovirus B19 infection (see Chapter 18), mycoplasma infections, and arthritis associated with bacterial infections. With bacterial infections the arthritis may be due to direct invasion, i.e., septic arthritis, or may occur as part of an immunological reaction to infection, as with \textit{Brucella} (see Section 16.2, p. 256) or \textit{Yersinia} infection. In some infections, such as meningococcal or Hib infections, it is not always clear whether the arthritis is due to direct invasion or due to a post-infectious inflammatory response. Post-infectious arthritis and rheumatic fever (see p. 25) are well-recognized with group A streptococcal infection.

### 11.7 Open fractures

A Cochrane review of seven studies (913 participants) of antibiotics for open fractures found that prophylactic antibiotics were associated with a reduction in the risk of infection (RR 0.41, 95% CI 0.27–0.63).\(^79\) The absolute risk reduction was 8% and 13 children had to be given antibiotics to prevent one infection. (95% CI 8–25).\(^79\) Although the Cochrane review did not compare different regimens, the data show that the antibiotic should have antistaphylococcal activity.

We recommend:

\[
\text{diclofenac/oxa/nafcinil } 50 \text{ mg/kg (max 2 g) IV, 6-hourly for 1–3 days OR}
\]
\[
\text{cephalothin } 50 \text{ mg/kg (max 2 g) IV, 6-hourly OR}
\]
\[
\text{cephazolin } 25 \text{ mg/kg (max 1 g) IV, 8-hourly}
\]

For patients with anaphylactic penicillin allergy, we recommend:

\[
\text{clindamycin } 10 \text{ mg/kg (max 450 mg) IV or orally, 8-hourly}
\]

The duration of prophylaxis should be longer (5–7 days) if presentation is delayed for 8 hours or longer. If bone infection is established, treat as for osteomyelitis (see p. 158).

If wound soiling or tissue damage is severe and/or devitalized tissue is present, we recommend:

\[
\text{piperacillin+tazobactam } 100 + 12.5 \text{ mg/kg (max 4 + 0.5 g) IV, 8-hourly OR}
\]
\[
\text{ticarcillin+clavulanate } 50 + 1.7 \text{ mg/kg (max 3 + 0.1 g) IV, 6-hourly FOLLOWED BY}
\]
\[
\text{amoxicillin+clavulanate } 22.5 + 3.2 \text{ mg/kg (max 875 + 125 mg) orally, 12-hourly}
\]

If there has been significant fresh- or saltwater exposure, we recommend:

\[
\text{ciprofloxacin } 10 \text{ mg/kg (max 400 mg) IV, 12-hourly OR}
\]
\[
\text{ciprofloxacin } 15 \text{ mg/kg (max 750 mg) orally, 12-hourly PLUS}
\]
\[
\text{clindamycin } 10 \text{ mg/kg (max 450 mg) IV or orally, 8-hourly}
\]
Osteomyelitis and septic arthritis

References


CHAPTER 12
Respiratory infections

12.1 Upper respiratory tract infections

Acute otitis media
Acute otitis media (AOM) is an acute infection of the middle ear, characterized by pain, fever, irritability, poor feeding, redness, and bulging of the tympanic membrane.\(^1\) AOM is one of the most frequent diseases in early infancy and childhood. Approximately 10% of children have an episode of AOM by 3 months of age. The peak age-specific incidence is between 6 and 15 months. AOM is common in infancy and in preschool years, is less common in school-age children, and is uncommon in healthy adults.\(^1\)

Children with defective humoral immunity, with low levels of IgG, IgG sub-class deficiency, or with poorly functioning IgG, often have recurrent AOM, implying that antibodies are an important host protection against otitis media. The main anatomic defects predisposing to recurrent AOM involve the palate and thus obstruct Eustachian tube drainage. Environmental factors include exposure to tobacco smoke. There is a group of “otitis-prone” children who get recurrent AOM, but have no identifiable immunologic or anatomic defect.\(^1\)

Diagnosis
Children with colds or viral upper respiratory tract infections (URTI) often have eardrums that look dull and move poorly using pneumatic otoscopy. If tympanocentesis is performed in children with colds or URTI, no middle ear fluid is obtained.\(^3\) In contrast, children with AOM usually have middle ear fluid, and if tympanocentesis is performed, bacteria can be isolated from 70 to 90% of middle ear cultures.\(^3\) Children with AOM have acute inflammation, with either erythema of the tympanic membrane or otalgia.\(^3\) AOM is different from otitis media with effusion (OME),\(^10\) which is a chronic condition characterized by middle ear effusion without acute inflammation.\(^3\) (see p. 169).

Tympanocentesis is commonly performed in the diagnosis and management of AOM in Scandinavian countries, sometimes in North America, and virtually never in the rest of Europe or Australia, because of concerns about pain and efficacy. Tympanocentesis has not been compared to antibiotics without tympanocentesis or to no treatment in RCTs. When AOM is diagnosed by otoscopy and tympanometry, tympanocentesis yields fluid in 85% of cases.\(^8\)\(^9\)

Tympanometry has 65–97% sensitivity in diagnosing AOM when compared to tympanocentesis.\(^2\)\(^10\) If the diagnosis of AOM is made on the otoscopic appearance, the single most important clinical finding associated with finding a middle ear pathogen in one study, with a sensitivity of 74%, is fullness or bulging of the tympanic membrane.\(^11\) Erythema of the eardrum is less helpful, but when cultures are negative, the drum is usually shiny, dull, or white.\(^11\) Pneumatic otoscopy is recommended in preference to simple otoscopy in order to detect effusions.\(^1\)

Organisms
Bacteria are found in 50–90% of children with AOM with or without otorrhea,\(^1\)\(^12\)\(^13\)\(^14\) viruses are found in 20–49% of cases, and coinfection with bacteria and viruses in 18–27%.\(^15\)\(^16\) The major bacterial pathogens in AOM are *Streptococcus pneumoniae*, untypeable *Haemophilus influenzae*, *Moraxella catarrhalis*, and in children >5 years, *Streptococcus pyogenes*. Although the proportions vary with age and geographic location, these organisms are consistently found.\(^1\)\(^12\)\(^13\)\(^14\) In places like North America, where pneumococcal conjugate vaccine is routinely given to infants, a shift in the proportion of the major AOM pathogens has been

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The antibiotics and doses recommended in this chapter are based on those in *Therapeutic Guidelines: Antibiotic*, 13th edn, Therapeutic Guidelines Ltd, Melbourne, 2006.
described so that *H. influenzae* now predominates. A study examined the correlation between nasopharyngeal bacteria and the bacteria obtained by tympanocentesis from children with AOM. The sensitivity and specificity were both 99% for pneumococci but not clinically useful for other bacteria.

Treatment of AOM

**Antibiotics for AOM: yes or no?**

**Question** | For children with AOM, do antibiotics compared with no antibiotics or placebo result in more rapid resolution of symptoms?

**Literature review** | We found 80 studies, 10 high-quality RCTs, a non-Cochrane meta-analysis, and a Cochrane systematic review.

A Cochrane review found 10 RCTs but only 8 high-quality trials (2287 children) that reported clinically relevant data. The trials showed no reduction in pain at 24 hours, but a 30% relative reduction (95% CI 19–40%) in pain after 2–7 days. Since approximately 80% of patients will have settled spontaneously in this time, this means an absolute reduction of 7% or that about 15 children must be treated with antibiotics to prevent one child having some pain after 2 days. The conclusion of the authors was that antibiotics provide a small benefit for AOM in children, and because about 80% cases will resolve spontaneously (the so-called Polynanna phenomenon, from an American book about a girl with a very optimistic approach that things always get better), the benefit from antibiotics must be weighed against the possible adverse reactions from antibiotics and risks of resistance.

A more inclusive meta-analysis that included 80 studies found very similar results. Children with AOM not treated with antibiotics experienced a 1–7-day clinical failure rate of 19% (95% CI 10–28%) and few supplicative complications. When patients were treated with amoxicillin, the 2–7-day clinical failure rate was reduced to 7%, a 12% reduction (95% CI 4–20%). There was no evidence to support any particular antibiotic regimen as more effective at relieving symptoms. Adverse effects, primarily gastrointestinal, were more common among children on cefixime than among those on ampicillin or amoxicillin, and more common among children on amoxicillin-clavulanate than among those on azithromycin.

Suppurative complications such as mastoiditis, which used to be common, are now rare, even without antibiotic treatment. A review of trials from 1966 to 1999 estimated the incidence of mastoiditis as 1 in 1000 children with untreated otitis media. In some countries, such as the Netherlands, only about 30% of children with AOM are treated with antibiotics and the rest with close observation.

**Antibiotics for AOM: delayed versus immediate prescription**

**Question** | For children with AOM, do delayed antibiotic prescriptions compared with immediate antibiotics reduce antibiotic use and do they result in increased morbidity?

**Literature review** | We found one high-quality RCT of delayed antibiotic prescription for AOM and a Cochrane review of delayed antibiotic prescription for various respiratory disorders in children.

Because of the emergence of antibiotic-resistant organisms and overuse of antibiotics for self-limiting viral URTIs, there have been a number of studies of delayed antibiotic prescriptions. Parents are given a prescription for antibiotics but advised to fill the prescription only if symptoms persist after 2–3 days.

We found one RCT in which children aged 6 months to 10 years with AOM seen in a UK general practice were randomized to immediate or delayed antibiotics. The delayed antibiotic group was instructed to collect an antibiotic prescription at the parents’ discretion after 72 hours if the child was not improving. On average, symptoms resolved after 3 days. Children prescribed antibiotics immediately improved more quickly. On average, their illness lasted 1 day less, they had a reduction in night disturbance of 0.7 of a night, and the paracetamol consumption was half a spoon a day less. There was no difference in school absence or pain or distress scores, since benefits of antibiotics occurred mainly after the first 24 hours when distress was less severe. Parents of 36/150 (24%) of the children given delayed prescriptions used antibiotics. Fewer children in the delayed group had diarrhea (9% versus 19%). The authors concluded that for children who are not very unwell systematically, a wait-and-see approach seems feasible and acceptable to parents and could substantially reduce the use of antibiotics for AOM.
The Cochrane review found seven studies, four of sore throat, two of viral respiratory tract infections, and the one of otitis media. For most outcomes there was no difference between immediate and delayed antibiotic groups, but patients in the delayed antibiotic group in three of the studies had significantly more fever.

**Duration of antibiotic treatment for AOM**

**Question** | For children with AOM, is treatment with antibiotics for 5 days as effective as treatment with antibiotics for longer?

**Literature review** | We found 33 RCTs, a non-Cochrane meta-analysis, and a Cochrane review.

A meta-analysis comparing fewer than 7 days of antibiotics with 7 or more days found that 44 children would need to be treated with the longer course of antibiotics to avoid one treatment failure. A Cochrane review of 33 studies (1524 children) by the same authors found a worse treatment outcome at 8–19 days in children treated with antibiotics for 5 days compared with 8–10 days (OR 1.52, 95% CI 1.17–1.98). By 20–30 days, however, outcomes were comparable. The absolute difference in treatment failure at 20–30 days suggests that at least 17 children would need to be treated with the long course of antibiotics to avoid one treatment failure. The authors concluded that 5 days of short-acting antibiotic use is effective treatment for uncomplicated AOM in children.

**Recommendations for antibiotic therapy for AOM**

**No antibiotics or delayed prescription**

Older children who do not have systemic features (vomiting and fever) are likely to have a good outcome, so the need for immediate antibiotics can be assessed on an individual basis. We recommend the following:

- For children aged 6 months and older with no systemic features, symptomatic treatment (analgesics for pain relief and antipyretics for high fever and irritability) for 2 days is an option. If symptoms persist after 2 days, we recommend reevaluating the patient and reconsidering antibiotic treatment (see below).
- An alternative for children aged 6 months and older without systemic symptoms is to give a delayed prescription for antibiotics with instructions on filling it after 48–72 hours if symptoms persist or returning for reevaluation if they get worse (it is wise to give an expiry date on the prescription to avoid use at a much later date).
- For children aged 6 months to 2 years managed as above, we recommend ensuring contact (visit or telephone) after 24 hours, at which time further observation or antibiotics should be considered.

**Immediate antibiotics**

- For children aged less than 6 months, we recommend treating with antibiotics immediately. This is because diagnosis can be difficult in this age group and because there is a greater risk of suppurative complications if treatment is delayed.
- For children with systemic features, such as vomiting and fever, immediate antibiotic therapy is indicated.

High-dose amoxicillin is recommended when the incidence of penicillin-insensitive pneumococci is high. We recommend:

amoxicillin 40–50 mg/kg (max 1 g) orally, 12-hourly for 5 days

If the incidence of penicillin-insensitive pneumococci is low, we recommend:

amoxicillin 15 mg/kg (max 500 mg) orally, 8-hourly for 5 days

OR (if compliance is likely to be a problem)

amoxicillin 30 mg/kg (max 1 g) orally, 12-hourly for 5 days

If the patient is allergic to penicillin, we recommend:

cefdinir 7 mg/kg (max 300 mg) orally, 12-hourly for 5 days OR

cefpodoxime 5 mg/kg (max 200 mg) orally, 12-hourly for 5 days OR

cefuroxime 15 mg/kg (max 500 mg) orally, 12-hourly for 5 days

Children who fail to respond to amoxicillin alone are likely to be infected with a beta-lactamase-producing organism, *H. influenzae* or *M. catarrhalis*. Amoxicillin-clavulanate contains clavulanic acid which inhibits beta-lactamase enzymes. Recommended treatment is:

Amoxicillin + clavulanate 22.5 + 3.2 mg/kg (max 875 + 125 mg) orally, 12-hourly for 5 days
If the patient still fails to respond to therapy, we recommend seeking expert advice.

**Decongestants and antihistamines**

**Question** | For children with AOM, do decongestants and/or antihistamines compared with no treatment or placebo reduce symptoms and speed recovery?

**Literature review** | We found 15 RCTs and a Cochrane review.25

A Cochrane review of 15 studies of decongestants and antihistamines for AOM found that decongestants or antihistamines alone had no benefit.25 Combined decongestant-antihistamine use was associated with a decreased incidence of persistent otitis media at 2 weeks, but no benefit for early cure rates, symptom resolution, prevention of surgery, or other complications. There was a five- to eightfold increased risk of side effects for those receiving an intervention, which reached statistical significance for all decongestant groupings. The authors concluded that the clinical significance was minimal, that study design may have biased the results, and that routine use of decongestants or antihistamines could not be recommended.25

**Recurrent AOM**

Possible underlying causes of recurrent AOM and risk factors should be considered. These include immune deficiency (usually humoral), passive smoke exposure (tobacco, wood fires), child care, allergic rhinitis, adenoid disease, and structural anomalies such as cleft palate.26

**Question** | For children with recurrent AOM, does tympanostomy tube insertion (grommets) or adenoectomy or prophylactic antibiotics compared with no treatment reduce the frequency of episodes of AOM?

**Literature review** | We found four RCTs of tympanostomy tube insertion,27–30 four RCTs of adenoectomy,31–34 and nine RCTs and a non-Cochrane meta-analysis35 of prophylactic antibiotics in which a placebo group was included.

Early small studies suggested that tympanostomy tubes were effective in reducing the number of episodes in children with recurrent AOM. The largest study of 264 children, however, found that tympanostomy tubes did not reduce the frequency of AOM compared with placebo, and 3.9% of children who received tubes developed persistent tympanic membrane perforations.30 The authors also pointed out that the incidence of AOM was far lower than predicted in the placebo group, so any intervention should be viewed in this light.

Early studies suggested some benefit from adenoidec- tomoy,31,32 but recent studies have found none, irrespective of whether adenoidec-tomy was performed alone33 or with tympanostomy tube insertion.34

A non-Cochrane meta-analysis of nine studies (958 subjects) found that antibiotic prophylaxis of recurrent otitis media reduced the incidence of AOM by 89% (95% CI 81–97%).35 Two studies found that antibi-otic chemoprophylaxis with amoxicillin reduced the frequency of episodes of AOM,30,36 but the benefits must be weighed against the dangers of inducing resistance and the natural history of resolution. Early studies found co-trimoxazole chemoprophylaxis to be effective, but more recent studies did not confirm this finding.33,37

**We do not recommend tympanostomy tubes or adenoectomy for children with recurrent AOM. Prophylactic amoxicillin is likely to be effective, but the benefits should be weighed against the risks of selecting for resistant organisms and of other adverse events.**

**Chronic OME (“glue ear”)**

Chronic OME is the persistence of middle ear effusion for more than 3 months. OME is very common in children, especially between the ages of 1 and 3 years with a prevalence of 10–30% and a cumulative incidence of 80% at the age of 4 years.38 The usual presentation is with symptoms attributable to hearing loss or pain.

Although many different interventions have been tried to improve short- and long-term hearing in children with chronic OME because of fears of the effect on language development, a meta-analysis of 38 studies found very little evidence that OME impairs later language development.38 Recommendations about interventions, particularly invasive procedures, should reflect the relatively benign outcome.

**Diagnosis of OME**

A systematic review of eight methods of diagnosing OME, including pneumatic otoscopy, tympanometry, and acoustic reflectometry, examined 52 studies.38
Pneumatic otoscopy performed best with a sensitivity of 94% (95% CI 92–96%) and a specificity of 80% (95% CI 75–86%). However, examiner qualifications were reported inconsistently, and training was not specified. The authors concluded that the finding that pneumatic otoscopy can do as well as or better than tympanometry and acoustic reflectometry has significant practical implications. For the typical clinician, pneumatic otoscopy should be easier to use than other diagnostic methods. The important question may be what degree of training will be needed for the clinician to be as effective with pneumatic otoscopy as were the examiners in the studies reviewed in this report. A practice guideline made a strong recommendation that clinicians use pneumatic otoscopy as the primary diagnostic method to distinguish OME from AOM.

Antibiotics for chronic OME

Question | For children with chronic OME, do antibiotics compared with no antibiotics or placebo speed resolution of effusion?

Literature review | We found 20 RCTs and 3 non-Cochrane meta-analyses.

Bacteria can be cultured from about 20 to 30% of chronic middle ear effusions. All the three meta-analyses found that antibiotics hasten short-term resolution of chronic OME, although a meta-analysis of eight studies found that they have no effect on long-term outcome. Because the aim is to speed short-term resolution without invasive intervention, a short course of antibiotics is a sensible first-line treatment option. Recommended treatment is:

- amoxicillin 40–50 mg/kg (max 1 g) orally, 12-hourly for 10–30 days
- amoxicillin 15 mg/kg (max 500 mg) orally, 8-hourly for 10–30 days

OR (if compliance is likely to be a problem)

- amoxicillin 30 mg/kg (max 1 g) orally, 12-hourly for 10–30 days

If the patient is allergic to penicillin, we recommend:

- cefdinir 7 mg/kg (max 300 mg) orally, 12-hourly for 10–30 days OR cefpodoxime 5 mg/kg (max 200 mg) orally, 12-hourly for 10–30 days OR cefuroxime 15 mg/kg (max 500 mg) orally, 12-hourly for 10–30 days

If the children fail to respond to amoxicillin, it may be that they are infected with a beta-lactamase-producing organism or that they would benefit from corticosteroids (see below). We recommend giving amoxicillin-clavulanate, with or without oral corticosteroids:

amoxicillin + clavulanate 22.5 + 3.2 mg/kg (max 875 + 125 mg) orally, 12-hourly for 10–30 days

Corticosteroids for chronic OME

Question | For children with chronic OME, do oral corticosteroids compared with no corticosteroids or placebo speed resolution of effusion?

Literature review | We found RCTs and a Cochrane review of oral corticosteroids.

Inflammation may contribute to persistent OME. Short, 7–14-day courses of oral corticosteroids have been used alone or in combination with antibiotics. A Cochrane systematic review found the OR for OME persisting after short-term follow-up in children treated with oral steroids compared with control was 0.22 (95% CI 0.08–0.63); i.e., there was a 78% reduction. The OR for OME persisting after short-term follow-up for children treated with oral steroids plus antibiotic compared with control plus antibiotic was 0.37 (95% CI 0.25–0.56). As with antibiotics, there was no evidence of long-term benefit.

We recommend that if a child has persistent OME despite a course of antibiotics, the option of giving oral corticosteroids with a second course of amoxicillin or amoxicillin-clavulanate should be strongly considered, and certainly before proceeding to surgery. We recommend:

- prednisolone 1 mg/kg orally, daily for 7–14 days

Ventilation tubes (grommets) for chronic OME

Question | For children with chronic OME, do ventilation tubes compared with no tubes reduce the short-term and long-term incidence of effusion and the incidence of hearing loss?
**Literature review** | We found 21 RCTs and a Cochrane review.43

The insertion of ventilation tubes or grommets is the operation most frequently performed on children in North America, Europe, and Australia. Despite its immense popularity, there is increasing evidence that this invasive operation has only very modest benefit. Children treated with grommets spend 32% less time with effusion in the next year, and their hearing levels improved by about 9 dB during the first 6 months and 6 dB at 12 months.43 The benefit is lost thereafter, and early insertion of grommets has no measurable effect on language development or cognitive function.43 There may be sub-groups who would benefit more from grommets, notably children with cleft palate or perhaps those attending day care,44 but there is no good evidence that this is the case. Furthermore, grommets are associated with significant adverse effects, including tympanosclerosis, tympanic membrane atrophy, and chronic ear discharge.45 In general, we recommend that conservative management with antibiotics and topical or systemic corticosteroids should be tried first, and even if unsuccessful, there is little evidence that the short-term benefits of grommets are outweighed by the risks.

**Antihistamines and decongestants for chronic OME**

**Question** | For children with chronic OME, do antihistamines and/or decongestants compared with no treatment or placebo result in more rapid resolution of effusion?

**Literature review** | We found 18 RCTs and a Cochrane review.45

A Cochrane review of 18 studies of antihistamines, decongestants, or antihistamine-decongestant combinations found no statistical or clinical benefit, and 11% of those who received active treatment reported adverse events.45 We recommend that these agents should not be used.

**Recommendations for specialist referral for OME**

We recommend specialist ENT referral in the following situations:

- Persistent effusion for >3 months, not responding to antibiotics with or without steroids, in a child with speech or educational delay;
- Persistent effusion for >3 months, not responding to antibiotics with or without steroids, in a child with bilateral hearing loss;
- Structural damage to the tympanic membrane (significant retraction, concern about possible cholesteatoma).

**Chronic suppurative otitis media (CSOM)**

**Question** | For children with CSOM, does aural toilet compared with no aural toilet reduce the duration of ear discharge?

**Literature review** | We found four reasonable quality RCTs of aural toilet, and the use of aural toilet was analyzed as part of a larger Cochrane review of interventions for CSOM.46

CSOM is primarily a disease of developing countries and of indigenous children living in Australia, North America, Northern Europe, and New Zealand.47 CSOM is due to an underlying eardrum perforation and needs to be distinguished from otitis externa (see p. 173) because both can result in purulent exudate in the external ear canal. In children with CSOM, regular aural toilet has been shown to be effective46,48 and is recommended prior to any topical treatment. Dry mopping with rolled tissue spears or an equivalent (repeated 6–12-hourly until the ear canal is dry) can be taught to family members. Suction kits for use under direct vision are very useful if training and equipment are available. Resolution may take some weeks.

**Question** | For children with CSOM, do topical antibiotics compared with no topical antibiotics reduce the duration of ear discharge?

**Literature review** | We found 14 RCTs and a Cochrane review.49

The use of topical antibiotics has been shown to speed resolution of CSOM.49 Topical quinolone antibiotics clear aural discharge better than no drug treatment,49 better than topical antiseptics,49 and better than oral antibiotics.50 Topical quinolones have not been shown to be superior to non-quinolone topical antibiotics.49 There are theoretical concerns about possible ototoxicity with the use of topical aminoglycosides, such
as gentamicin or framycetin. Evidence suggests that short-term use is safe, even in the presence of a non-intact tympanic membrane (including grommets).\textsuperscript{49} Use of topical aminoglycosides for more than 7 days in children with tympanic perforations is not advised.

The addition of steroids to topical antibiotics has not been studied well. In one small RCT of Australian Aboriginal children, topical ciprofloxacin was superior to topical framycetin plus dexamethasone in terms of resolution of otorrhea, although follow-up was short.\textsuperscript{51} The use of topical quinolones may select for resistant bacteria,\textsuperscript{52} but this risk has to be balanced against the theoretical risk of ototoxicity of topical aminoglycosides. A systematic review of topical antibiotics and resistance found no good evidence that topical antibiotics induce resistance, but the development of resistance has not been well studied, and the evidence that they do not induce resistance was weak.\textsuperscript{53} Topical quinolones should be used if there has been no response to first-line therapy after 7 days. Recommended treatment is:

- **regular ear toilet (as above) AND EITHER ciprofloxacin 0.3% ear drops, five drops into the affected ear, 12-hourly for up to 9 days OR dexamethasone 0.05% + framycetin 0.5% + gramicidin 0.005% ear drops, three drops into the ear 6-hourly for not longer than a total of 7 days**

Persistent discharge may require more prolonged courses of preparations not containing aminoglycosides. Topical quinolones should be used if there has been no response to dexamethasone plus framycetin after 7 days.

Although systemic antibiotics offer no advantage over topical antibiotics for CSOM,\textsuperscript{49,50} if aural discharge is from a recent perforation (i.e., within the last 6 weeks), we recommend oral antibiotics to treat AOM (see p. 168) as well as topical treatment.

In severe persistent cases, referral to an ENT specialist is recommended for more detailed examination and to exclude cholesteatoma or chronic mastoiditis (see p. below).

**Mastoiditis**

Mastoiditis is an infection of the air cells within the mastoid bone. It is a complication of otitis media and occurs because the mucoperiosteal lining of the mastoid is continuous with that of the middle ear.\textsuperscript{54} Mastoiditis may be acute or chronic.

**Acute mastoiditis**

Acute mastoiditis is now rare in industrialized countries. A systematic review estimated the incidence of mastoiditis as 1 in 1000 children with untreated otitis media.\textsuperscript{20} The diagnosis of acute mastoiditis is clinical. Children presented with redness or swelling behind the ear, which is pushed forward, and associated with redness and bulging of the tympanic membrane.\textsuperscript{55} Other features include pain, fever, and irritability. Complications include CNS (central nervous system) involvement with meningitis or lateral sinus thrombosis, and lower motor neurone facial palsy.\textsuperscript{55–59}

Because of its rarity, immune deficiency, particularly humoral (antibody production), should be strongly considered in a young child with acute mastoiditis in an industrialized country. Initial investigations should at least include a blood count and serum immunoglobulin and IgG sub-class levels, while B- and T-cell subsets may also be indicated if there is a suggestion that defective antibody production is second to a T-cell defect.

The organisms isolated from the middle ear of children with acute mastoiditis are not quite the same as for AOM. The commonest in order of frequency are *S. pneumoniae, S. pyogenes, and Staphylococcus aureus.*\textsuperscript{55–59} Less common isolates are *H. influenzae, Gram-negative bacilli, enterococci, anaerobes*, and even *Mycobacterium tuberculosis.*\textsuperscript{55–59}

The recommended management is surgical drainage of the middle ear, usually involving tympanocentesis followed by myringotomy or tympanostomy tubes (grommets), plus antibiotics. We recommend:

- **cefotaxime 25 mg/kg (max 1 g) IV, 8-hourly PLUS di/fluc/oxa/nafcinil 50 mg/kg (max 2 g) IV, 6-hourly**

For children with CNS involvement, particularly when meningitis is suspected and LP contraindicated, to cover penicillin-resistant pneumococci we recommend:

- cefotaxime 25 mg/kg (max 1 g) IV, 8-hourly PLUS vancomycin 15 mg/kg (max 500 mg) IV, 6-hourly

**Chronic mastoiditis**

Chronic mastoiditis is associated with CSOM (see p. 171). There is chronic infection of the mastoid air cells, which may result in sub-periosteal abscess,
chronic osteomyelitis, cholesteatoma, and intracranial suppuration. The diagnosis should be suspected in any child with chronic suppurative ear discharge. The diagnosis can be confirmed and extent of damage delineated by computed tomography and magnetic resonance imaging scan. 60

The organisms most commonly isolated are different from acute mastoiditis. Gram-negative bacilli, including *Pseudomonas*, are the most frequent, followed by *S. aureus* and anaerobes. 51–63

The treatment is combined surgical and medical. We recommend ENT consultation. We could find no RCTs of antibiotic treatment. For severe infections, to cover the likely pathogens, 61–63 we recommend:

**gentamicin <10 years:** 7.5 mg/kg; **≥10 years:** 6 mg/kg IV, daily PLUS EITHER

- ticarcillin-clavulanate 50 + 1.7 mg/kg (max 3 + 0.1 g) IV, 6-hourly OR
- piperacillin-tazobactam 100 + 12.5 mg/kg (max 4 + 0.5 g) IV, 8-hourly

Where there is extracranial extension, particularly when *Pseudomonas* is likely, we recommend using, on its own:

**cefe pime 50 mg/kg (max 2 g) IV, 8-hourly**

**Otitis externa**

Otitis externa is a form of infected eczema which often follows persistent exposure of the ear canals to water. *Pseudomonas aeruginosa* and *S. aureus* are the most common organisms isolated, as well as other Gram-negative bacilli and occasionally fungi. We found 17 RCTs of topical treatment of otitis externa in children. Topical antibiotics and topical corticosteroids were equally effective, but were not compared with placebo or no treatment.

We recommend that a health professional should remove debris or exudate by dry aural toilet, using mechanical suction under direct vision or by dry mopping with a cotton wool swab. The ear canal should not be syringed with water. Dry cleaning should be followed by instillation of topical corticosteroid and antibiotic combination drops. Recommended treatment is:

- **dexamethasone 0.05%+fran mycin 0.5%+gramicidin 0.005% ear drops**, three drops instilled into the ear, thrice daily for 3–7 days
- **flumethasone 0.02%+c atquin 1% ear drops**, three drops instilled into the ear, twice daily for 3–7 days

It is recommended to keep the ear dry for 2 weeks after treatment. More severe cases may be treated by insertion of a wick soaked in the corticosteroid and antibiotic combination. Indications for systemic antibiotics include fever, spread of inflammation to the pinna, and local folliculitis.

If otitis externa recurs, it may help to keep the ear canals dry using earplugs and shower caps during showering and swimming, and/or using Vaseline or other water repellents, e.g., placing a few drops of isopropyl alcohol in the ear canals after swimming.

**Common cold and purulent rhinitis**

The common cold is caused by viruses. Characteristically, it causes clear nasal discharge, which becomes mucopurulent and persists for about 5–7 days. Although bacteria can often be isolated from the mucopurulent nasal discharge, this does not indicate whether they are colonizing the nose or causing the discharge. Just because a child has green mucus, it does not mean that antibiotics should be given.

**Antibiotics and the common cold**

**Question** | For children with colds, do antibiotics compared with no antibiotics or placebo reduce the duration of purulent rhinitis or prevent complications?

**Literature review** | We found seven RCTs, a Cochrane review, 64 and a more recent meta-analysis by the Cochrane authors. 65

The Cochrane analysis of six trials in adults and children found that antibiotics were no better than placebo in terms of cure or persistent symptoms, and adult patients who received antibiotics had significantly more adverse effects. 64 An updated meta-analysis 65 by the same authors found seven trials, four with data on benefits and four with data on harms of antibiotics. At 5–8 days antibiotics were beneficial (RR 1.18, 95% CI 1.05–1.33), with 7–15 patients needing to be treated to benefit one. Antibiotics caused a significant increase in adverse events (RR 1.46, 95% CI 1.10–1.94), mostly gastrointestinal effects. Although antibiotics are probably effective for acute purulent rhinitis, they can cause harm, usually in the form of gastrointestinal effects.
Most patients will get better without antibiotics. We feel the significant adverse effects outweigh the modest benefits.

**We do not recommend antibiotics for children with colds, even if they have purulent rhinitis.**

**Vitamin C and the common cold**

**Question** | For normal children, does prophylactic vitamin C prevent the common cold or reduce its severity? For children with colds, does treatment with vitamin C compared with no vitamin C or placebo reduce the duration or severity of illness?

**Literature review** | We found 30 RCTs, a non-Cochrane meta-analysis, and a Cochrane review\(^6\) on prophylaxis. We found 7 RCTs on treatment of common colds with vitamin C and the same Cochrane review\(^6\) also looked at treatment effects of vitamin C.

The Cochrane review of 29 RCTs of vitamin C prophylaxis, using ≥200 mg/day of vitamin C, found no overall benefit of prophylactic vitamin C in reducing the incidence of colds.\(^6\) Twelve of the prophylaxis studies included children. However, prophylaxis shortened the duration of colds by about a day in children taking prophylactic vitamin C (from 7 to 6 days) and their colds were less severe.\(^6\) A sub-group of 6 trials that involved a total of 642 adult marathon runners, skiers, and soldiers on subarctic exercises reported a pooled RR of 0.50 (95% CI 0.38–0.66). The consistent and statistically significant small benefits on duration and severity for those using regular vitamin C prophylaxis indicates that vitamin C plays some role in respiratory defense mechanisms. In a study of Navajo schoolchildren, prophylactic vitamin C had no effect on incidence, severity, or duration of colds, but children with high plasma ascorbic acid concentrations had longer mean illness (6.8 days versus 4.0 days, \(p < 0.05\)) than those with low levels.\(^6\) This suggests that high doses of vitamin C might have harmful effects. Mega-dose vitamin C supplementation is discouraged because it is potentially harmful. Low-dose vitamin C prophylaxis or emphasizing the importance of citrus fruit or fresh orange juice for children is justified by the data. Vitamin C supplementation could also be justified in children exposed to brief periods of severe physical exercise, such as elite athletes.

Starting treatment with vitamin C after symptoms of a cold developed did not reduce the incidence or duration of colds in adults or children and is not recommended.\(^6\)

**Antihistamines and nasal decongestants and the common cold**

**Question** | For children with colds, do antihistamines and/or nasal decongestants compared with no treatment or placebo reduce the duration or severity of illness?

**Literature review** | We found 22 RCTs of antihistamines alone, 5 of decongestants, and 13 of combined treatment with antihistamines and decongestants. We found a Cochrane review of antihistamines\(^6\) and a Cochrane review of decongestants.\(^6\)

Antihistamines alone did not alleviate nasal congestion, rhinorrhea, or sneezing in children or adults, while first-generation antihistamines increased drowsiness.\(^6\) Decongestants alone have not been studied in children and are not recommended for young children with colds.\(^6\) A single dose is moderately effective for short-term relief of nasal congestion in adults, but repeated use has not been shown to be beneficial.\(^6\) Antihistamine–decongestant combinations are ineffective in young children.\(^6\) In adults and older children, they show a small benefit in general recovery, and in nasal symptoms, of doubtful clinical significance.\(^6\)

**We do not recommend antihistamines, decongestants, or antihistamine–decongestant combinations for children with colds.**

**Zinc and the common cold**

**Question** | For children with colds, does zinc compared with no treatment or placebo reduce the duration or severity of illness?

**Literature review** | We found 15 RCTs, a Cochrane review,\(^7\) and a non-Cochrane meta-analysis\(^7\) of zinc lozenges.

A Cochrane review of 10 studies of zinc gluconate lozenges for treatment of colds found no overall benefit on duration or severity.\(^7\) However, a meta-analysis\(^7\) showed a trend toward benefit with a non-significant reduction in symptoms at 7 days (OR 0.52, 95% CI 0.25–1.2), so a very large study might show a significant
benefit. Subsequent studies of zinc lozenges have not confirmed any benefit. The only study in children found no benefit in terms of duration or severity of colds, but the zinc group had significant adverse effects of bad taste, mouth, tongue, or throat discomfort, nausea, and diarrhea.\(^7\)

**We do not recommend zinc for children with colds.**

**Sinusitis**

Imaging studies have shown that about 40% of children\(^7\) and a greater proportion of adults\(^7\) with colds have changes consistent with sinusitis after 7 days. Most of the changes will resolve spontaneously.\(^7\) Persistence of nasal symptoms and cough beyond 10 days in children has been suggested as an indicator of a probable diagnosis of acute sinusitis.\(^7\) In a study of 2013 children with respiratory complaints, 135 had persistent symptoms after 10 days and 92.5% of the 135 had radiologic changes of sinusitis.\(^7\) Fever >39°C and purulent nasal discharge increase the probability of severe sinusitis. Bad breath is often reported, but facial pain and headache are less common in children.\(^7\)

Imaging for sinusitis is controversial. Plain radiographs (Waters’ view) looking for sinus opacification, air-fluid level, or marked mucosal thickening have a high sensitivity in children with persistent respiratory symptoms (88% in one study\(^7\)) but low specificity, because asymptomatic radiologic sinus changes are common. There is no need to use computerized tomography, with its increased radiation and the significant attendant risk of malignancy, in the vast majority of children with suspected acute or chronic sinusitis. The combination of typical acute or chronic symptoms together with typical changes on plain radiographs merits a trial of antibiotics (see below).

**Question**  | For children with acute sinusitis, do antibiotics compared with no antibiotics or placebo reduce the duration or severity of symptoms?

**Literature review** | We found 49 RCTs and a Cochrane review\(^7\) of antibiotic use in adults with acute maxillary sinusitis. We found only 3 RCTs of antibiotics in children with acute sinusitis. We found 6 RCTs and a Cochrane review\(^7\) of antibiotics for children with persistent nasal discharge. The definition of sinusitis and the quality of the studies varied.

In a Cochrane review of 49 RCTs of antibiotics for acute maxillary sinusitis in adults and children,\(^7\) penicillin improved clinical cure rates compared to controls (RR 1.72, 95% CI 1.00–2.96) and there was a trend for amoxicillin to be effective (RR 2.06, 95% CI 0.65–6.53) but wide confidence intervals. Radiographic outcomes were improved by antibiotic treatment. Comparisons between classes of antibiotics showed no significant differences between antibiotics. Compared to amoxicillin-clavulanate, dropouts due to adverse effects were significantly lower for cephalosporin antibiotics (RR 0.47, 95% CI 0.30–0.73). Relapse rates within 1 month of successful therapy were 7.7%. We found only 3 RCTs in children with acute sinusitis which compared antibiotics with placebo.\(^7\)

A small RCT of children with radiologically confirmed sinusitis found that children treated with either amoxicillin or amoxicillin-clavulanate were more likely to be cured (67 and 64%, respectively) than children treated with placebo (43%).\(^7\) A larger study of children with clinical sinusitis treated with the same antibiotics found no benefit,\(^7\) and a study of cefuroxime for radiologic sinusitis was likewise negative.\(^8\)

A Cochrane review of children with nasal discharge persisting for at least 10 days\(^7\) found six studies (562 children). They concluded that for children with persistent nasal discharge or older children with radiographically confirmed sinusitis, the available evidence suggests that antibiotics given for 10 days will reduce the probability of persistence in the short to medium term. They found that the benefits were modest and around 8 children must be treated in order to achieve one additional cure (NNT 8, 95% CI 5–29).

We conclude that there is evidence of modest benefit in treating children with radiologically confirmed acute sinusitis with antibiotics. The organisms causing sinusitis are the same as those causing AOM. Recommended treatment is:

amoxicillin 40–50 mg/kg (max 1 g) orally, 12-hourly for 7–14 days

If penicillin-insensitive pneumococci are rare, we recommend:

amoxicillin 15 mg/kg (max 500 mg) orally, 8-hourly for 7–14 days
OR (if compliance is likely to be a problem) amoxicillin 30 mg/kg (max 1 g) orally, 12-hourly for 7–14 days

If the patient is allergic to penicillin, we recommend: cefdinir 7 mg/kg (max 300 mg) orally, 12-hourly for 7–14 days OR cefpodoxime 5 mg/kg (max 200 mg) orally, 12-hourly for 7–14 days OR cefuroxime 15 mg/kg (max 500 mg) orally, 12-hourly for 7–14 days

Children who fail to respond to amoxicillin alone are likely to be infected with a beta-lactamase-producing organism, *H. influenzae* or *M. catarrhalis*. Amoxicillin-clavulanate contains clavulanic acid which inhibits beta-lactamase enzymes. Recommended treatment is:

amoxicillin + clavulanate 22.5 + 3.2 mg/kg (max 875 + 125 mg) orally, 12-hourly for 7–14 days

**Acute tonsillitis or pharyngitis**

Acute sore throat is most often caused by viral infections. It is difficult to distinguish clinically between viral and bacterial causes of sore throat. A bacterial cause of acute sore throat, almost always group A streptococcus (GAS) (*S. pyogenes*), is more common in children aged 3–13 years (30–40%) than in children aged less than 3 years (5–10%) or adults (5–15%).

**Question** For children with acute sore throat or tonsillitis, do antibiotics compared with no antibiotics or placebo shorten the duration of illness or reduce the frequency of complications?

**Literature review** We found 27 RCTs of antibiotic treatment for sore throat or tonsillitis and a Cochrane review.

A Cochrane systematic review of antibiotics for sore throat found 27 studies, but only 3 were exclusively in children. Throat soreness and fever were reduced by antibiotics by about one half. The greatest difference was seen at about 3–4 days (when the symptoms of about 50% of untreated patients had settled). By 1 week about 90% of treated and untreated patients were symptom-free. Antibiotics are effective: just under six people with a sore throat need to be treated with penicillin rather than placebo to cure one extra sore throat at day 3 (this is sometimes referred to as the “number needed to treat” or NNT = 6). Antibiotics are far more effective in those who have culture-confirmed streptococcal sore throats, with symptoms significantly reduced after both 3 and 7 days. Interestingly, however, antibiotics were associated with a significant reduction in symptoms at day 3 even if the swab was negative for GAS (RR 0.78, 95% CI 0.63–0.97), suggesting that other bacteria may be important causes of sore throat.

Antibiotics compared to placebo reduced the incidence of AOM (RR 0.30, 95% CI 0.15–0.58), of acute sinusitis (RR 0.48, 95% CI 0.08–2.76), and of quinsy or peritonsillar abscess (RR 0.15, 95% CI 0.05–0.47), which occurs in 1–2% of untreated episodes of tonsillitis.

Several studies found that antibiotics reduced acute rheumatic fever by more than three quarters (RR 0.22, 95% CI 0.02–2.08). Acute rheumatic fever is now rare in industrialized countries, where the annual incidence of rheumatic fever (<1 case per 100,000) is greatly exceeded by the risk of a severe reaction to penicillin (15–40 per 100,000 treatment courses). Prevention of rheumatic fever remains important in developing countries, but is no longer the main indication for antibiotic treatment of streptococcal pharyngitis in industrialized countries, except in high-risk populations such as indigenous communities.

The Cochrane review found a trend for antibiotics to protect against acute glomerulonephritis, but there were insufficient cases to be certain. In order to reduce antibiotic use, it would be helpful to find ways of limiting antibiotic use to children with sore throat who are most likely to benefit, mainly those with streptococcal sore throat. Culture of a throat swab or use of a reliable rapid detection kit are the most reliable ways to diagnose the presence of GAS, although even this has problems because some children may be chronic carriers of GAS but have a coincidental viral sore throat. Culture results are not available for 24–48 hours. Treatment options are to decide whether to give antibiotics immediately on the basis of a rapid test, to wait for a culture result, to treat empirically, to give a delayed prescription, or to give no antibiotics. The decision about which children to treat empirically might be helped by clinical criteria, such as a scoring system, or laboratory criteria, such as rapid antigen detection tests.
Clinical criteria for diagnosis of streptococcal tonsillopharyngitis

Clinical scoring systems improve the accuracy of identifying a patient as having a streptococcal sore throat. The best known are the Centor criteria\textsuperscript{83}: an adult with sore throat who has fever, absence of cough, swollen tender anterior cervical lymph nodes, and tonsillar erythema and exudate has a >80% chance of having a streptococcal sore throat.\textsuperscript{85} However, <10% of adults with sore throat meet these four criteria, so the criteria are not very useful in the day-to-day management of patients with sore throat.

The McIsaac clinical score, based on the Centor criteria but with an age weighting, is more appropriate for children, with a sensitivity of 96.9% for diagnosing group A streptococcal infection in children aged 3–14 years (see Box 12.1).\textsuperscript{84} Using these criteria, 59% of patients would have been considered at low risk (total score 0 or 1 point) and not treated with antibiotics and no swab sent, while 10.5% had the highest score (4 or 5 points) and would be treated with antibiotics immediately. A swab would be sent on the remaining 30% of patients and antibiotics given only if positive. The authors of the study reported that the proportion of patients receiving initial antibiotic prescriptions would have been reduced by 48% by following these score-based recommendations compared with observed physician prescribing ($p < 0.001$) without any increase in throat culture use.\textsuperscript{84}

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<thead>
<tr>
<th>Box 12.1 McIsaac scoring system for assessing sore throat.\textsuperscript{84}</th>
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<tr>
<td><strong>Add points to give total score</strong></td>
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<tr>
<td>Total score 0 or 1 point</td>
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<tr>
<td>Total score 2 or 3 points</td>
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<tr>
<td>Total score 4 or 5 points</td>
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Temperature > 38°C 1 point
No cough 1 point
Tender anterior cervical lymphadenopathy 1 point
Tonsillar swelling or exudate 1 point
Age 3–14 years 1 point

Rapid diagnosis of group A streptococcal infection

Rapid antigen detection tests are frequently used in pediatric practice in North America. When the likelihood of streptococcal sore throat is low, they have not been shown to be cost-effective, but they are more cost-effective if the risk is higher, e.g., a child aged 3–15 years old with sore throat, tonsillar erythema, and no cough.\textsuperscript{85}

Antibiotic for sore throat: yes or no?

Because of the need to reduce unnecessary antibiotic use, it is not recommended to treat children with sore throat with empiric antibiotics without taking a throat swab for rapid diagnosis or culture.

We recommend empiric antibiotic therapy after taking a swab for the following indications:

- tonsillitis with 4 or 5 days of fever >38°C, no cough, tender anterior cervical lymphadenopathy, tonsillar swelling, or exudate, age 3–14 years;
- patients aged 3 years and older with sore throat in communities with a high incidence of acute rheumatic fever (e.g., some Australian Aboriginal and native American communities);
- existing rheumatic heart disease at any age;
- scarlet fever;
- peritonsillar cellulitis or abscess (quinsy).

Empiric antibiotic therapy is not recommended for:

- children <3 years old, even with fever and exudate, because viral infection, e.g., adenovirus, is much more likely;
- children with suspected glandular fever.

Which antibiotic for sore throat, not laboratory-confirmed as due to GAS?

About 90% of adults and 70% of children with sore throat do not have streptococcal pharyngitis.\textsuperscript{81, 82} There are several reasons for preferring oral penicillin as empiric treatment for sore throat, which is suspected but not confirmed by laboratory testing to be group A streptococcal:
· If six children are treated with antibiotics instead of no antibiotic, one extra child will be free of sore throat 3 days later.\textsuperscript{82}
· Most sore throats improve anyway: 90% of treated and untreated patients are free of symptoms by 1 week.\textsuperscript{82}
· Penicillin is less likely to select for resistance than broader spectrum agents such as cephalosporins and macrolides.
· Penicillin is superior to placebo, cheap, and effective.
· Twelve-hourly phenoxyethylpenicillin is effective in streptococcal pharyngitis\textsuperscript{86} and is recommended because of greater compliance than with more frequent dosing regimens.

Recommended treatment for unproven streptococcal sore throat:

\textbf{phenoxyethylpenicillin 10 mg/kg (max 500 mg) orally, 12-hourly}

It is recommended that the penicillin be stopped after 24–48 hours if the throat swab does not grow a pathogenic streptococcus.

In poorly compliant patients or those intolerant of oral therapy, recommended treatment is:

\textbf{benzathine penicillin: child 3 to < 6 kg: 225 mg; 6 to <10 kg: 337.5 mg; 10 to <15 kg: 450 mg; 15 to <20 kg: 675 mg; >20 kg: 900 mg (1.5 million U) IM, as single dose}

For patients allergic to penicillin, it is safe to give cephalosporins.\textsuperscript{87} Recommended treatment:

\textbf{cefeuroxime 15 mg/kg (max 500 mg) orally, 12-hourly for 10 days OR azithromycin 20 mg/kg (max 600 mg) orally, daily for 3 days\textsuperscript{88} OR roxithromycin 4 mg/kg (max 150 mg) orally, 12-hourly for 10 days}

Which antibiotic for laboratory-proven group A streptococcal infection?

\textbf{Question} | For children with proven group A streptococcal infection, is any class of antibiotics compared with other antibiotics more effective? For children with proven group A streptococcal infection, is 5 days of antibiotics as effective as 10 days in terms of cure?

\textbf{Literature review} | We found 35 RCTs and 1 meta-analysis\textsuperscript{89} comparing cephalosporins and penicillin in children. We found 22 RCTS and 1 meta-analysis\textsuperscript{90} comparing short course (4–5 days) with 10 days of antibiotics.

Meta-analyses in adults\textsuperscript{91} and children\textsuperscript{89} have shown that cephalosporins are more effective than penicillin for bacteriologic and clinical cure of group A streptococcal tonsillitis/pharyngitis. In 1998, the USFDA, in providing guidance for the pharmaceutical industry, stated that any antibiotic evaluated for efficacy in group A streptococcal tonsillitis/pharyngitis must have a bacterial eradication rate of $\geq 85\%$ (www.fda.gov/cder/guidance/index.htm). A meta-analysis in children\textsuperscript{91} and a meta-analysis of shortened durations of antibiotic therapies compared to 10 days penicillin for this infection\textsuperscript{90} did not find a single study since 1990, in which the bacterial cure rate was $\geq 85\%$ using 10 days of penicillin. The change in bacteriologic efficacy for the penicillins has occurred despite the fact that \textit{S. pyogenes} remains highly susceptible to penicillin.\textsuperscript{92} Among the most widely noted explanations for this reduction in penicillin efficacy is the presence of increased frequency of beta-lactamase-producing normal flora in the tonsillipharynx (so-called copathogenicity) driven by antibiotic overuse.\textsuperscript{92} These copathogens (\textit{H. influenzae}, \textit{Morax. catarrhalis}, \textit{S. aureus}, and mouth anaerobes) are thought to shield or protect \textit{S. pyogenes} from eradication in vivo despite its continued in vitro activity. The copathogen explanation has only circumstantial supportive evidence.

We conclude that for laboratory-proven \textit{S. pyogenes} tonsillitis/pharyngitis, use of a cephalosporin has a strong evidence base. Because no differences have been shown among first-, second-, and third-generation cephalosporins in \textit{S. pyogenes} eradication, we recommend use of first-generation agents.

Recommended treatment for proven streptococcal sore throat:

\textbf{cephalexin 20 mg/kg (max 500 mg) orally, 12-hourly for 10 days}

In poorly compliant patients, recommended treatment is to shorten duration:

\textbf{cefpodoxime 5 mg/kg (max 200 mg) orally, 12-hourly for 5 days OR}
Which antibiotic for laboratory-proven group A streptococcal infection in a population at high risk for rheumatic fever?

Some populations, particularly children in developing countries and indigenous children in industrialized countries such as native Americans, Australian Aborigines and Maori, and Pacific Islanders in New Zealand, are at very high risk of rheumatic fever. They are also at increased risk of other non-suppurative complications of group A streptococcal infections, such as glomerulonephritis. A Cochrane review has shown that antibiotic treatment of acute streptococcal sore throat reduces the risk of acute rheumatic fever by 78% (RR 0.22, 95% CI 0.02–2.08).82 All these studies were almost done using penicillin to treat streptococcal sore throat. There have been no studies comparing cephalosporins with penicillin for prevention of acute rheumatic fever. For this reason, many authorities working with disadvantaged populations at high risk of rheumatic fever continue to recommend penicillin to treat sore throat.

In this case, recommended treatment for streptococcal sore throat is:

- phenoxymethylpenicillin 10 mg/kg (max 500 mg) orally, 12-hourly for 10 days

In poorly compliant patients or those intolerant of oral therapy, recommended treatment is:

- benzathine penicillin: child 3 to <6 kg: 225 mg; 6 to <10 kg: 337.5 mg; 10 to <15 kg: 450 mg; 15 to <20 kg: 675 mg, >20 kg: 900 mg IM, as single dose

Glandular fever (infectious mononucleosis)

Primary infection with Epstein-Barr virus and occasionally other viruses may be associated with severe pharyngitis. Antibiotics are not routinely indicated. Some reports have suggested an association between glandular fever and group A streptococcal infection, although the role of antibiotics in such cases is unclear. Amoxicillin and ampicillin are contraindicated in glandular fever because they frequently precipitate a severe rash. This is usually not an indication of penicillin hypersensitivity. Parenteral corticosteroids are often recommended if there is imminent airways obstruction, although without formal evidence. We found no studies on the effect of corticosteroids on airways obstruction. We found one RCT on the effect of dexamethasone on pain in exudative tonsillitis due to infectious mononucleosis.93 A single dose of dexamethasone 0.3 mg/kg (max 15 mg) orally reduced pain at 12 hours, but not later. Narcotic analgesics are contraindicated in glandular fever because of the danger of respiratory obstruction.

Recurrent pharyngitis and/or tonsillitis

**Question** | For children with recurrent tonsilopharyngitis, do antibiotics compared with no antibiotics or placebo reduce the frequency of episodes? For children with recurrent tonsilopharyngitis, does tonsillectomy compared to non-surgical treatment reduce the frequency of episodes?

**Literature review** | We found six RCTs that compared different antibiotic regimens but had no placebo group and four RCTs that compared antibiotic prophylaxis with placebo.94–97 We found three RCTs98–100 and a Cochrane review101 that compared tonsillectomy with no surgery.

The literature on recurrent pharyngitis and/or tonsillitis is sparse. We found only four RCTs with weak methodology comparing antibiotics with placebo for recurrent tonsillitis. Two studies suggested that benzathine penicillin reduced the incidence of group A streptococcal infections,94,95 one showed that azithromycin was ineffective96 and one showed that cefpodoxime reduced the frequency of sore throats.97 On the basis of the limited evidence, we recommend prophylactic antibiotics are not used because of lack of proof of efficacy and because of concerns about inducing antibiotic resistance. We recommend that each individual episode be treated as discussed on pp. 177–8).

A Cochrane review of tonsillectomy for recurrent tonsillitis found only two trials and is out of date.101 A study of “severely affected” children who had seven or more well-documented, clinically important, adequately treated episodes of throat infection in the preceding year, or five or more such episodes in each of the two preceding years, or three or more such episodes in each of the three preceding years, found that tonsillectomy reduced the number and severity of subsequent episodes of throat infection for at
least 2 years. On the other hand, in each follow-up year many subjects in the non-surgical groups had fewer than three episodes of infection, and most episodes among subjects in the non-surgical groups were mild. Surgery-related complications occurred in 14% of children and were reported as readily managed or self-limited. The authors conclude that their results warrant the election of tonsillectomy for children meeting the trial’s stringent eligibility criteria, but also provide support for non-surgical management. For mild to moderately affected children with fewer infections, most have very few infections in the next year without surgery and the at-best modest benefits of surgery do not appear to justify the risks. We recommend considering tonsillectomy only for the most severely affected children with recurrent tonsillitis.

**Croup (acute laryngotraceobronchitis)**

Croup or viral laryngotraceobronchitis presents with a coryzal prodrome, hoarseness (or husky voice in those old enough to speak), inspiratory or biphase stridor, and a barking “brassy” or seal-like cough. Children with concurrent large airways involvement are wheezy. Croup is caused by viruses, most commonly parainfluenza viruses, but also other respiratory viruses including rhinoviruses, respiratory syncytial virus (RSV), and influenza. Croup is most common in 1–3-year-old children and is generally self-limiting, with a duration of 2–5 days. Some children get recurrent episodes of spasmodic croup, which can have an allergic basis. Antibiotics are not indicated for croup.

In mild cases, no treatment is necessary, but we strongly recommend early reevaluation. It should be remembered that croup often gets worse at night.

In moderate to severe cases (e.g., a history of very noisy breathing at night, difficulty with breathing, or the presence of stridor on examination) corticosteroids are often used and epinephrine (adrenaline) or humidification may be added. Is there evidence for these interventions?

**Question** | For children with acute laryngotraceobronchitis (croup), do inhaled or systemic corticosteroids compared with no steroids or placebo reduce the duration or severity of illness? Does inhaled epinephrine (adrenaline) compared with no epinephrine or placebo improve outcome? Do mist tents or humidification of air compared with no treatment improve outcome?

**Literature review** | We found 31 RCTs and a Cochrane review of corticosteroid therapy for croup or laryngotraceobronchitis. We found 7 RCTs of epinephrine and 4 RCTs and a Cochrane review of mist or humidification.

A Cochrane review of 31 RTCs found that glucocorticoid treatment was associated with an improvement in clinical score at 6 and 12 hours, but this improvement was no longer significant at 24 hours. Patients treated with glucocorticoids were half as likely to return to hospital or be readmitted. On average, steroid-treated patients spent 12 hours less in accident and emergency or hospital.

Nebulized epinephrine is superior to placebo for short-term relief of croup symptoms (three studies) and is comparable in efficacy to nebulized budesonide.

Mist tents were not found in a Cochrane review of three RCTs or a later study to provide any significant benefit in croup.

Various corticosteroid regimens have been employed.

Examples include:

- dexamethasone 0.3 mg/kg orally or IV OR prednisolone or prednisone 1 mg/kg orally OR budesonide 2 mg by nebulizer

Repeat doses are usually not required, but can be considered if response to single-dose therapy is suboptimal at 24 hours. Failure to respond may rarely be due to bacterial tracheitis.

In more severe cases with significant airway obstruction or fatigue, treatment in hospital may be required with an initial dose of nebulized epinephrine. Recommended treatment is:

- epinephrine (adrenaline) 0.05 mL/kg/dose (max 0.5 mL) of 1:100 solution diluted up to 3 mL OR 0.5 mL/kg/dose (max 5 mL) 1:1000 solution, by nebulizer PLUS EITHER dexamethasone 0.6 mg/kg orally (or IM or IV if vomiting) OR prednisolone or prednisone 1 mg/kg orally

Maintenance doses and frequency vary with the severity of the condition and the response to treatment.
Hydrocortisone should not be used due to lack of evidence and short duration of action.

**Influenza**

Influenza is caused by influenza A and B viruses. The risk of catching influenza can be reduced by immunization, which needs to be given annually because of regular mutation of the virus (“antigenic drift”). Recommendations on which children should be routinely immunized vary from children at increased risk of severe disease, e.g., children with cyanotic congenital heart disease or chronic lung disease, to recommending that all children be immunized annually.

During influenza epidemics, children with fever > 38° and cough have a high probability of influenza, but other viral infections can present identically. The decision to use antivirals should preferably be based on proof of influenza infection, e.g., positive immunofluorescence of nasopharyngeal secretions for influenza. Amantadine and rimantadine are effective and inexpensive but are only active against influenza A strains. They may be cost-effective during times when public health antibiotics have identified influenza A as the strain circulating during a season. Neuraminidase inhibitors, which are effective against both strains, reduce the duration of illness by just over a day in previously healthy children and reduce the time to return to normal activity. Oseltamivir reduces complications of influenza, particularly otitis media. Zanamivir is currently given by inhalation only, limiting its use to older children. Treatment with a neuraminidase inhibitor is of no benefit unless commenced within 48 hours of the patient developing symptoms. Resistance is an increasing problem and has emerged during therapy. For this reason, although prophylaxis with neuraminidase inhibitors is effective in adults, we do not recommend prophylaxis of children outside a pandemic situation. If treatment is given, we recommend:

- **oseltamivir 2 mg/kg (max 75 mg) orally, 12-hourly for 5 days OR**
- **zanamivir (child > 5 yr) 10 mg by inhalation, 12-hourly for 5 days**

Antibacterials are not indicated in an otherwise healthy person. In those at special risk (e.g., children with chronic heart or lung disease) secondary bacterial infection may require treatment as for community-acquired pneumonia, using antibiotics active against staphylococcal as well as pneumococcal pneumonia.

Avian influenza is caused by a sub-type of influenza A virus. It is occasionally transmitted to humans via close contact with infected birds (especially chickens, but also ducks and geese). Occasional cases of human-to-human transmission have been reported (at the time of writing). There is the possibility of further virus mutation resulting in increased human-to-human transmission, with the potential for an influenza pandemic. If avian influenza is suspected, the local health department must be notified. Information is available from the World Health Organization (WHO) and the Centers for Disease Control (CDC) Web sites:


**Pertussis**

Pertussis (whooping cough) is caused by *Bordetella pertussis* and occasionally by *Bordetella parapertussis*. Other organisms such as viruses and *Chlamydia* can cause a pertussis-like illness. Pertussis generally manifests as a persistent illness, usually afebrile, characterized by one or more of:
- paroxysms of coughing;
- inspiratory whoop without other apparent cause;
- post-tussive vomiting;
- persistent cough lasting more than 2 weeks.

A nasopharyngeal aspirate should be sent for culture and/or polymerase chain reaction (PCR) testing. Serology can be very helpful in older children and young adults. It is much less useful in infants, for whom direct detection of the organism in a nasopharyngeal aspirate is the diagnostic modality of choice. Relevant public health authorities should be notified of cases of clinical or proven pertussis.

**Treatment of pertussis**

**Question** For children with pertussis, do antibiotics compared with no antibiotics or placebo reduce infectivity or reduce symptoms?

**Literature review** We found 10 RCTs and a Cochrane review of antibiotic treatment.

A Cochrane review found 10 antibiotic treatment trials of variable quality. Short-term antibiotics
(azithromycin for 3 days, clarithromycin for 7 days, or erythromycin estolate for 7 days) were as effective as long-term antibiotic treatment (erythromycin estolate or erythromycin for 14 days) in eradicating *B. pertussis* from the nasopharynx, and there were fewer side effects with short-term treatment. Neither short- nor long-term antibiotics altered the subsequent clinical course of the illness. Azithromycin is preferred to erythromycin in babies <1 month old because of a reported association between erythromycin and hypertrophic pyloric stenosis.111 Recommended treatment is:

- **azithromycin child <6 months**: 10 mg/kg orally, daily for 5 days
- **child ≥6 months**: 10 mg/kg (max 500 mg) orally on day 1, then 5 mg/kg (max 250 mg) orally, daily for a further 4 days OR
- **clarithromycin child >1 month**: 7.5 mg/kg (max 500 mg) orally, 12-hourly for 7 days OR
- **erythromycin child >1 month**: 10 mg/kg (max 250 mg) orally, 6-hourly for 7 days

**Prophylaxis against pertussis**

**Question** | For children exposed to pertussis, do prophylactic antibiotics compared with no antibiotics or placebo prevent infection?

**Literature review** | We found two studies and a Cochrane review110 of prophylactic antibiotics.

A Canadian study of household contacts found that erythromycin estolate prevented culture-positive pertussis in household contacts of patients with pertussis but did not prevent clinical pertussis.112 The Cochrane review found only two studies and concluded that there is insufficient evidence to determine the benefit of prophylactic treatment of pertussis contacts.110 Current recommendations for chemoprophylaxis of all household and child contacts with erythromycin or another macrolide are made despite the lack of evidence of efficacy. Prophylaxis is probably most justified for unimmunized or partially immunized babies <6 months old, because they have the highest risk of severe disease,109 and so any benefits are likely to outweigh harms of treatment. If giving chemoprophylaxis, the regimens (including duration) for prophylaxis are the same as for treatment (see pp. 181–2).

It is important to check the immunization status of children in the household and to catch up missed doses of pertussis vaccine.

**Prevention of pertussis**

Prevention is primarily through immunization with either whole cell pertussis vaccines or acellular vaccines, which contain three or more purified components of *B. pertussis*. In unimmunized populations, pertussis infects mainly schoolchildren, who in turn may infect babies <6 months who are at greatest risk of death or complications.109 A primary childhood course plus one or more booster doses protect against pertussis for a number of years. However, continued circulation of *B. pertussis*, with adults as an important source of childhood infections, has caused many countries to consider immunizing adolescents and adults, for whom acellular vaccines are highly immunogenic.113

**Lower respiratory tract infections**

**Bronchiolitis**

Bronchiolitis is the name of a pathologic condition (inflammation of the bronchioles) which is often used to describe a clinical entity.114 In Europe and Australia, the term is used to describe children <18 months old and usually <1 year with a clinical illness characterized by cough, crackles (with or without wheeze), and hyperinflation, and with radiographic changes of hyperinflation and patchy consolidation.114 In North America, the term is often used for a child <2 years old with an acute episode of wheeze (with or without crackles) during the RSV season (fall to mid-winter), which means there is considerable overlap with asthma.114 This means that clinical studies need to be interpreted bearing in mind these differences in definition.

RSV causes over 70% of episodes of bronchiolitis, with the rest caused by other viruses, including rhinovirus, human metapneumovirus, parainfluenza, and influenza viruses.114 RSV is the major respiratory pathogen of young children and the major cause of lower respiratory infections in infants. The peak incidence is between 1 and 6 months of age. It occurs worldwide, with annual epidemics in winter or in the rainy season in temperate climates. RSV is transmitted by close contact with contaminated fingers or fomites, but may also be spread by coarse aerosols produced
by coughing or sneezing. The attack rate can be extremely high in day-care centers. Babies with chronic cardiorespiratory disease, babies born prematurely, the immunocompromised, and the elderly are at increased risk of severe RSV infection.\textsuperscript{114}

Death from bronchiolitis is extremely rare and is usually due to hypoxia. The modern use of pulse oximetry to monitor oxygenation has resulted in better use of supplemental oxygen and improved survival.\textsuperscript{114}

Treatment of bronchiolitis

Ribavirin for bronchiolitis

**Question** | In babies with bronchiolitis, does nebulized ribavirin compared with placebo or no treatment reduce clinical severity or duration of hospitalization?

**Literature review** | We found 12 RCTs and a Cochrane review.\textsuperscript{115}

Initial excitement about the role of nebulized ribavirin in treating RSV infection has been tempered by the realization that the benefits are at best marginal\textsuperscript{115} and offset by concerns about toxicity to staff, notably potential teratogenicity for pregnant women, and about cost. The vast majority of infants with RSV bronchiolitis recover without treatment. The cumulated results of three small trials on ventilated patients suggest that ribavirin may reduce the duration of mechanical ventilation by a mean of 1.8 days, but trials have not been able to show reductions in duration of hospitalization or in mortality.\textsuperscript{115} Long-term follow-up studies have not shown any benefit in terms of pulmonary function or incidence of recurrent wheezing.\textsuperscript{115}

We do not recommend nebulized ribavirin either for ventilated or for unventilated children with RSV bronchiolitis, but we recommend considering nebulized ribavirin to treat children with severe defects of immunity, e.g., oncology patients or children with T-cell immunodeficiency.

Bronchodilators for bronchiolitis

**Question** | In babies with bronchiolitis, do bronchodilators compared with placebo or no treatment reduce clinical severity or duration of hospitalization?

**Literature review** | We found 22 RCTs and a Cochrane review.\textsuperscript{116}

Analysis of the role of bronchodilators in bronchiolitis is complicated by the definitional problems described above. A Cochrane review of 22 clinical trials (1428 infants) with bronchiolitis found a statistically significant but clinically modest improvement in the overall average clinical score with bronchodilator use, but no significant improvement in oxygenation. Bronchodilator recipients showed no improvement in the rate of hospital admission after treatment as outpatients or duration of hospitalization for inpatients. The authors acknowledged that the inclusion of studies that enrolled infants with recurrent wheezing might have biased the results in favor of bronchodilators.\textsuperscript{116}

We do not recommend bronchodilators for children with bronchiolitis.

Epinephrine (adrenaline) for bronchiolitis

**Question** | In babies with bronchiolitis, does nebulized epinephrine (adrenaline) compared with bronchodilators or placebo or no treatment reduce clinical severity or duration of hospitalization?

**Literature review** | We found 14 RCTs and a Cochrane review.\textsuperscript{117}

A Cochrane review\textsuperscript{117} of 14 studies comparing epinephrine with placebo or bronchodilators found minimal evidence of benefit and some evidence of harm by causing increased pallor and tachycardia. Limited evidence suggested that outpatient use of nebulized epinephrine might be favorable compared with salbutamol and placebo, but the benefits were minor and there was no reduction in hospital admission.\textsuperscript{117}

We do not recommend nebulized epinephrine for children with bronchiolitis.

Corticosteroids for bronchiolitis

**Question** | In babies with bronchiolitis, do systemic corticosteroids compared with placebo or no treatment reduce clinical severity or duration of hospitalization?

**Literature review** | We found 13 RCTs and a Cochrane review of systemic corticosteroids.\textsuperscript{118}

A Cochrane review of 13 trials (1198 children) showed no benefit of systemic (oral, IM, or IV) corticosteroids in acute bronchiolitis.\textsuperscript{118}
We do not recommend systemic corticosteroids for children with bronchiolitis.

Chest physiotherapy for bronchiolitis
A Cochrane review of three studies found no evidence that chest physiotherapy improves outcome in children <2 years with bronchiolitis.119

Surfactant for mechanically ventilated children with bronchiolitis
A Cochrane review found three studies of surfactant for 79 babies being mechanically ventilated for bronchiolitis.120 Surfactant decreased duration of mechanical ventilation by 2.6 days and duration of intensive care by 3.3 days, although the reviewers felt that the studies have overestimated the benefits.

Antibiotics for bronchiolitis

**Question** | In children with acute bronchiolitis, do antibiotics compared with no antibiotics or placebo improve outcome?

**Literature review** | We found two poor-quality RCTs and no meta-analyses.

The incidence of bacteremia is <1% in RSV bronchiolitis and even lower (<0.5%) in children without risk factors for severe RSV infection.121 We could find only one RCT of ampicillin or placebo for babies with bronchiolitis.122 The main outcome, duration of illness, was no different.122 In another RCT of antibiotics for children with pneumonia or bronchiolitis from any cause, antibiotics had no effect on outcome in an RSV-positive sub-group.123 Although there is weak evidence that antibiotics are unnecessary and no evidence of benefit, antibiotics are frequently prescribed for children with bronchiolitis and often continued even when the child is known to be RSV-positive.121

We do not recommend antibiotics routinely for children with bronchiolitis.

Children are more likely to be bacteremic if they have nosocomial RSV infection (6.5% of all RSV infections in one study121), cyanotic congenital heart disease (6.6%), or are admitted to intensive care (2.9%), and so empiric antibiotic therapy might be considered for these groups until cultures are back.121 The organisms causing bacteremia are most often *S. pneumoniae, H. influenzae*, and *S. aureus*.121

If antibiotics are used, we recommend:

- **cefotaxime** 25 mg/kg IV, 8-hourly OR
- **ceftriaxone** 25 mg/kg IV, daily until culture results are available

Prevention of bronchiolitis
There are no effective RSV vaccines currently available, although there has been much recent research on live attenuated vaccines and sub-unit vaccines, which may be licensed in future.

**RSV immunoglobulin**
Hyperimmune polyclonal RSV immunoglobulin derived from blood donations has been shown to reduce the incidence of RSV hospitalization and admission to the intensive care unit, but not mechanical ventilation, when given prophylactically to babies and infants with bronchopulmonary dysplasia and to preterm babies without bronchopulmonary dysplasia.124 RSV immunoglobulin is contraindicated in children with congenital heart disease because it caused severe cyanotic episodes and poor outcome after surgery. It is expensive, has to be given by monthly infusion, and is not readily available.

**Palivizumab**
A humanized mouse monoclonal antibody to RSV, palivizumab, is more effective and less costly than RSV immunoglobulin, but its cost is still very high. It is given by IM injection each month during periods of anticipated risk of RSV. It reduces the risk of hospitalization from about 10% to about 5% for both preterm babies, babies with bronchopulmonary dysplasia, and babies with congenital heart disease.124,125 It has not been shown to decrease the risk of mechanical ventilation for RSV infection, to reduce long-term morbidity, or to save lives.

**Question** | For babies at increased risk of severe RSV infection, is palivizumab compared to no treatment cost-effective?

**Literature review** | We found nine cost-effectiveness analyses of palivizumab.

We found nine cost-effectiveness analyses of palivizumab. None of them found that palivizumab was cost-effective, even for selected babies at high risk of severe RSV infection, such as extremely low-birth
weight babies or babies with congenital heart disease. Despite the lack of evidence of cost-effectiveness, the American Academy of Pediatrics recommends its use for selected high-risk babies. We do not feel that the evidence supports the use of palivizumab unless cost is not a consideration.

We do not recommend the use of palivizumab.

**Acute bronchitis**

**Question** | For children with acute bronchitis, do antibiotics compared to no antibiotics or placebo speed recovery?

**Literature review** | We found eight RCTs of antibiotic use for acute bronchitis in children and a Cochrane review. Acute bronchitis is inflammation of the major bronchi and sometimes trachea, causing cough, and usually associated with an acute viral URTI. A Cochrane review found that antibiotics reduce cough and feeling ill by about half a day, statistically but probably not clinically significant. We recommend that children with acute bronchitis should not be given antibiotics routinely.

**Chronic bronchitis**

There is a group of children with recurrent moist cough who do not have bronchiectasis or asthma. The exact prevalence is unknown, but the prevalence of chronic cough reported in a large European study was 3% of school-aged children and 9% in the preschool-age group. A Cochrane review found only two moderate quality RCTs (140 children) comparing 7 days treatment with erythromycin or amoxicillin-clavulanate with placebo. Antibiotic treatment reduced the proportion of children not cured at follow-up (OR 0.13, 95% CI 0.06–0.32), which mean that only three children needed to be treated to cure one. Although the data are weak, antibiotics are likely to be beneficial in the treatment of children with chronic moist cough.

**Pneumonia**

In neonates, most early-onset pneumonia (in the first 2–3 days after birth) is caused by organisms acquired from the maternal perineal flora, with group B streptococcus (S. agalactiae) and Gram-negative bacilli the most common pathogens. After the neonatal period, most cases are viral in origin, but bacterial pneumonia can occur and may be life-threatening.

**Diagnosis of pneumonia**

Pneumonia is a clinical and radiologic diagnosis. In infants, tachypnea, fever, and cough are the cardinal signs, but one or more may be absent in pneumonia. Additional signs of respiratory distress (chest recession, grunting, nasal flaring) may be present. There are few clinical signs or symptoms that distinguish viral from Mycoplasma from bacterial pneumonia. The most reliable distinguishing sign is wheeze, which is strongly correlated with viral pneumonia. However, Mycoplasma pneumoniae and Chlamydia pneumoniae can also cause a pneumonitis which presents with wheeze, and although these organisms classically affect children >5 years old, they can also cause disease in children aged 2–5 years.

**Community-acquired pneumonia**

**Organisms causing community-acquired pneumonia**

S. pneumoniae is the commonest cause of acute bacterial pneumonia in children. The evidence for this statement does not come from positive laboratory data, because positive blood cultures are rare in pneumonia and the significance of elevated pneumococcal antibody titers is uncertain. The best evidence comes from the reduction in the incidence of pneumonia that followed the introduction of effective pneumococcal vaccines. The incidence of radiologic pneumonia fell by about 20% after the introduction of conjugate pneumococcal vaccines, which is a reasonable evidence that 20% of radiologic pneumonia was due to pneumococci. This has been called the “vaccine probe” measure of the incidence of a disease. Less common causes of pneumonia include non-typeable H. influenzae (particularly in those with underlying lung disease), H. influenzae type b in unimmunized populations, M. pneumoniae, C. pneumoniae, and S. aureus. C. trachomatis should be considered in febrile infants up to 3 months of age with cough and pneumonitis, particularly if there is concomitant eye discharge and/or a history of maternal vaginal discharge (both present in about 50% of cases).
Investigations for community-acquired pneumonia

Blood cultures are recommended but are positive in only about 10% of children with pneumonia. If pleural fluid is present, it should be aspirated, if possible, for diagnostic purposes. Rapid antigen testing for viruses using immunofluorescent techniques or ELISA can be very helpful, but finding a virus does not exclude mixed viral and bacterial infections. Acute viral serology is generally unhelpful, although finding a single high *M. pneumoniae* titer on an acute serum sample can direct therapy. Bacterial antigen testing and bacterial serology are largely unhelpful in management decisions.

Antibiotic treatment of community-acquired pneumonia

Treatment will depend on local epidemiology and on availability of antibiotics. Antibiotic regimens should be as narrow as possible to treat the likely organisms. These include *S. pneumoniae* and *H. influenzae*, while it may be necessary to use antibiotics effective against *S. aureus* and *M. pneumoniae*.

*S. aureus* pneumonia is rare but severe. It is characterized by systemic toxicity and often radiographic changes of empyema and/or pneumatoceles. If *S. aureus* pneumonia is suspected, empiric therapy should include antistaphylococcal antibiotics (see p. 188). The possibility of community-acquired MRSA (cMRSA) should be considered whenever *S. aureus* is suspected, especially in risk groups for cMRSA, such as Maori-Polynesian or other indigenous groups.

*M. pneumoniae* infection is more common once school age is reached.

Oral antibiotics are preferred in mild pneumonia and are used to complete the treatment in more serious cases. Children with moderate to severe pneumonia usually require parenteral therapy, at least initially. Infants and children with preexisting cardiac or pulmonary disease require earlier and more intensive treatment than previously healthy children.

The following recommendations are based on consensus opinion because good evidence is not available.

**Birth to 1 week**

The pneumonia is usually caused by a maternally acquired pathogen. Recommended treatment is:

- benzylpenicillin 60 mg (100,000 U)/kg IV, 12-hourly for 7 days PLUS
- gentamicin 2.5–3 mg/kg (<30 weeks’ gestation) OR 3.5 mg/kg (>30 weeks’ gestation) IV, daily for 7 days

[NB: Herpes simplex virus (HSV) pneumonitis may present between days 3 and 7. The diagnosis can be made by sending a nasopharyngeal aspirate for rapid diagnosis using HSV immunofluorescence and viral culture. If positive for HSV, treat with:

- acyclovir 20 mg/kg IV, 8-hourly for 14 days (21 days if encephalitis also present)]

**1 week to <4 months**

Treatment for *C. trachomatis* and *Bord. pertussis* should be considered at this age. If patient is afebrile and only mildly or moderately ill, recommended treatment is:

- azithromycin 10 mg/kg orally, daily for 5 days OR (if child >1 month old)
- clarithromycin 7.5 mg/kg orally, 12-hourly for 7 days OR
- erythromycin 10 mg/kg orally or IV, 6-hourly for 7–14 days.

[In babies <1 month old, erythromycin is not recommended because of concerns that it may cause pyloric stenosis, and clarithromycin is not recommended because safety data are not available.]

If the patient is febrile or *C. trachomatis* has been excluded, use:

- benzylpenicillin 30 mg (50,000 U)/kg IV, 6-hourly for 7 days

For severe disease (systemic toxicity and/or oxygen dependence), use:

- cefotaxime 25 mg/kg IV, 8-hourly for 7 days OR
- cefuroxime 50 mg/kg 2 g IV, 6-hourly for 7 days

If *S. aureus* is confirmed, see “Staphylococcal pneumonia,” below.

**4 months to <5 years**

Most cases are viral, but because it is difficult to exclude bacterial infection, particularly pneumococcal infection, antibacterial therapy is recommended.
For mild disease, recommended treatment is:

**amoxicillin 45–50 mg/kg (max 1 g) orally,**
12-hourly for 7 days

If penicillin-insensitive pneumococci are rare, we recommend:

**amoxicillin 15 mg/kg (max 500 mg) orally,**
8-hourly for 5 days
OR (if compliance is likely to be a problem)

**amoxicillin 30 mg/kg (max 1 g) orally,** 12-hourly for 5 days

If the patient is allergic to penicillin, we recommend:

**cefdinir 7 mg/kg (max 300 mg) orally,** 12-hourly for 5 days OR
**cefpodoxime 5 mg/kg (max 200 mg) orally,** 12-hourly for 5 days OR
**cefuroxime 15 mg/kg (max 500 mg) orally,** 12-hourly for 5 days

For moderate disease (e.g., lobar or lobular consolidation, pleural effusion), children should be hospitalized and treatment should also cover atypical organisms (M. *pneumoniae*, C. *pneumoniae*). Recommended treatment is:

**benzylpenicillin 30 mg (50,000 U)/kg IV,**
6-hourly for 7 days PLUS EITHER
**azithromycin 10 mg/kg orally,** daily for 5 days OR
**roxithromycin 4 mg/kg orally,** 12-hourly for 7 days

For severe disease (large pleural effusion, systemic toxicity, and/or oxygen dependence), we recommend hospitalization and treatment using:

**ceftaxime 25 mg/kg IV,** 8-hourly for 7 days OR
THE COMBINATION OF
**ceftiraxone 25 mg/kg IV,** daily for 7 days PLUS
di/flucl/oxa/nafcillin 50 mg/kg IV, 6-hourly for 7 days

The addition of cover against atypical organisms should be considered. We recommend:

**azithromycin 10 mg/kg/day IV,** daily for 7 days

If staphylococcal pneumonia is suspected on clinical grounds (e.g., very severe disease, large pleural effusion, pneumatoceles) or ethnicity (increased incidence in Maori-Polynesian, Aboriginal, and other indigenous children), see “Staphylococcal pneumonia,” below.

### 5–15 years

While *S. pneumoniae* is the commonest organism, *M. pneumoniae* is also prominent in this age group, but occurs in 3–4-yearly epidemics.

For mild disease, recommended treatment:

**amoxicillin 45–50 mg/kg (max 1 g) orally,**
12-hourly for 7 days

If penicillin-insensitive pneumococci are rare, we recommend:

**amoxicillin 15 mg/kg (max 500 mg) orally,**
8-hourly for 7 days
OR (if compliance is likely to be a problem)

**amoxicillin 30 mg/kg (max 1 g) orally,** 12-hourly for 7 days

If the patient is allergic to penicillin, we recommend:

**cefdinir 7 mg/kg (max 300 mg) orally,** 12-hourly for 7 days OR
**cefpodoxime 5 mg/kg (max 200 mg) orally,** 12-hourly for 7 days OR
**cefuroxime 15 mg/kg (max 500 mg) orally,** 12-hourly for 7 days

If also intending to treat for *M. pneumoniae* or *C. pneumoniae*, we recommend adding:

**azithromycin 10 mg/kg (max 400 mg) orally,**
daily for 5 days OR
**clarithromycin 7.5 mg/kg (max 250 mg) orally,**
12-hourly for 7 days OR
**roxithromycin 4 mg/kg (max 150 mg) orally,**
12-hourly for 7 days

For more serious disease, we recommend hospitalization, and using:

**benzylpenicillin 30 mg (50,000 U)/kg (max 1.2 g or 2 million U) IV,** 6-hourly for 7 days PLUS
**azithromycin 10 mg/kg (max 400 mg) orally,**
daily for 5 days OR
**clarithromycin 12.5 mg/kg (max 500 mg) orally,**
12-hourly for 7 days OR
**roxithromycin 4 mg/kg (max 150 mg) orally,**
12-hourly for 7 days
Staphylococcal pneumonia

Staphylococcal pneumonia may occur as a primary infection or secondary to right-sided endocarditis, influenza, measles, or aspiration. It is commonly severe in children and may be either community- or hospital-acquired.

Recently, there has been an increase in the incidence of severe community-acquired pneumonia caused by community strains of MRSA, in many parts of the world. These strains are more prevalent in some populations (e.g., intravenous drug users and indigenous children) and are genetically distinct from hospital-acquired MRSA strains. Sometimes they are clinically more aggressive, causing severe soft tissue infections and necrotizing pneumonia, generally because they carry the gene for the virulence factor, Panton-Valentine leukocidin. They are usually susceptible to macrolides, such as clindamycin, and to trimethoprim-sulfamethoxazole. Appropriate susceptibility testing of all *S. aureus* isolates is crucial. Antibiotic therapy for these new cMRSA strains should be guided by microbiologic susceptibility data, and specialist advice may be necessary. In contrast, in many other clinical settings, the presence of *S. aureus* or MRSA in sputum culture may simply represent colonization.

For non-MRSA staphylococcal pneumonia, recommended treatment is:

- **di/flucl/oxa/nafcillin 50 mg/kg (max 2 g) IV, 6-hourly** OR
- **cephalothin 50 mg/kg (max 2 g) IV, 6-hourly** OR
- **cephazolin 25 mg/kg (max 1 g) IV, 8-hourly**

When cMRSA is suspected, e.g., because child from ethnic group with high incidence or because of accompanying soft tissue infection, recommended treatment is:

- **clindamycin 10 mg/kg (max 450 mg) IV, 8-hourly**

For patients with immediate penicillin hypersensitivity and severely ill patients with suspected staphylococcal pneumonia, until antibiotic susceptibility data are available, recommended treatment is:

- **vancomycin <12 years: 30 mg/kg (max 1 g) IV, 12-hourly, 12 years or older: 25 mg/kg (max 1 g) IV, 12-hourly**

For severely ill patients with suspected MRSA staphylococcal pneumonia, vancomycin should be given together with the beta-lactam regimen until susceptibility data are known. We recommend:

- **vancomycin <12 years: 30 mg/kg (max 1 g) IV, 12-hourly, 12 years or older: 25 mg/kg (max 1 g) IV, 12-hourly** TOGETHER WITH
- **di/flucl/oxa/nafcillin 50 mg/kg (max 2 g) IV, 6-hourly** OR WITH
- **cephalothin 50 mg/kg (max 2 g) IV, 6-hourly** OR WITH
- **cephazolin 25 mg/kg (max 1 g) IV, 8-hourly**

It is usually possible to complete antibiotic therapy with oral antibiotics, based on sensitivities if available. A suitable oral antibiotic for non-MRSA pneumonia would be:

- **cefuroxime 10 mg/kg (max 500 mg) orally, 12-hourly**

For cMRSA, if sensitive, we recommend:

- **clindamycin 10 mg/kg (max 450 mg) orally, 8-hourly** AND
- **rifampicin 10 mg/kg (max 400 mg) orally, daily**

Trimethoprim-sulfamethoxazole is an alternative agent to treat susceptible cMRSA.

The optimum duration of therapy is unknown and may vary from child to child, but 7–14 days is usually effective.

Although some recent studies have suggested that linezolid may be more effective than vancomycin in patients with MRSA pneumonia, these studies suffer from significant flaws in methodology. Vancomycin, therefore, remains the treatment of choice for MRSA pneumonia, except for pneumonia caused by vancomycin-intermediate strains of *S. aureus* (VISA or hetero-VISA) when linezolid should be used.

Hospital-acquired pneumonia

Hospital-acquired or nosocomial pneumonia is defined as pneumonia that is not incubating at the time of admission to hospital and develops in a patient hospitalized for longer than 48 hours. Pneumonia in immunocompromised patients will be considered separately, below.

The pathogens causing hospital-acquired pneumonia differ from those causing community-acquired
pneumonia. Hospitalized patients frequently develop oropharyngeal colonization with Gram-negative bacilli and may also be exposed to multiresistant hospital pathogens such as methicillin-resistant *S. aureus* (MRSA), and multi-drug-resistant (MDR) organisms including enterobacteria, *P. aeruginosa*, *Acinetobacter* species, and *Stenotrophomonas maltophilia*. RSV infection is usually acquired from hands of staff. Other respiratory viruses and fungi that can be inhaled are potentially important causes. Prevention of nosocomial pneumonia is complex and has been addressed in a consensus guideline.139

**We recommend that antibiotics are not justified in the following situations:**

- When bacteria are cultured from sputum or endotracheal aspirates, but the child does not have pneumonia: this represents colonization only and does not justify a diagnosis of hospital-acquired pneumonia;
- When there is post-operative atelectasis: this should be managed with physiotherapy, and antibiotic therapy is not indicated, irrespective of sputum culture results;
- When a child with asthma has temporary atelectasis.

In the presence of pneumonia, sputum culture may give some indication of the bacterial agent(s) responsible and their antibiotic susceptibilities, although the accuracy of sputum culture in predicting the organisms causing pneumonia has not been proven. Use of bronchoalveolar lavage, endotracheal aspirates, and protected specimen brush can be valuable in identifying organisms and may provide evidence to stop or reduce therapy with broad-spectrum antibiotics.

Therapy can be stratified according to the risk of acquiring MDR organisms:

**Low risk of MDR organisms**: Patients hospitalized in a low-risk ward for any duration or short-term <5 days in a high-risk area (e.g., intensive care) should have therapy aimed at *S. pneumoniae* and non-MDR Gram-negative bacilli.

For low-risk patients with mild disease (well enough to take oral antibiotics), we recommend:

**amoxicillin + clavulanate 22.5 + 3.2 mg/kg**

(max 875 + 125 mg) orally, 12-hourly for 7 days

If patient is unable to take oral therapy, we recommend:

**benzylpenicillin 30 mg (50,000 U)/kg**(max 1.2 g or 2 million U) IV, 6-hourly PLUS

**gentamicin <10 years: 7.5 mg/kg; ≥10 years: 6 mg/kg IV, daily**

We recommend to switch to amoxicillin + clavulanate (as above) when patient is able to tolerate oral therapy.

In mildly ill patients allergic to penicillin, recommended treatment is:

**cefuroxime 10 mg/kg (max 500 mg) orally,**

12-hourly for 7 days OR

**moxifloxacin 10 mg/kg (max 400 mg) orally,**

daily for 7 days

For patients with moderate to severe pneumonia, recommended treatment is:

**ceftriaxone 25 mg/kg (max 1 g) IV, daily** OR

**cefotaxime 25 mg/kg (max 1 g) IV, 8-hourly** OR

**ticarcillin + clavulanate 50 + 1.7 mg/kg (max 3 + 0.1 g) IV, 6-hourly** OR THE COMBINATION OF

**benzylpenicillin 30 mg (50,000 U)/kg**(max 1.2 g or 2 million U) IV, 6-hourly PLUS

**gentamicin <10 years: 7.5 mg/kg; ≥10 years: 6 mg/kg IV, daily**

We recommend switching to oral therapy (as for patients with mild disease) when there has been significant improvement.

In patients with anaphylactic penicillin allergy, recommended treatment is:

**moxifloxacin 10 mg/kg (max 400 mg) orally or IV,**

daily for 7 days

**High risk of MDR organisms**: Patients hospitalized for 5 days or longer in high-risk areas are more likely to have MDR infection. Because survival is improved by early appropriate therapy, a broader-spectrum initial regimen is recommended.

There is little published evidence to guide treatment options. The following regimens are likely to be equivalent, but local protocols should be developed based on the sensitivities of local colonizing and infecting organisms. When broad-spectrum antibiotics are used, their use should be reviewed regularly and they should be stopped as soon as possible. There is evidence that the response to
appropriate antimicrobial therapy for ventilator-associated pneumonia occurs within the first 6 days and that prolonged therapy results in colonization and reinfection with resistant organisms. Treatment for 7 days is recommended, except for *P. aeruginosa, Acinetobacter* species, or *S. maltophilia* when up to 14 days’ treatment may be needed.

For patients with hospital-acquired pneumonia in high-risk wards (e.g., intensive care unit, high-dependency units, known specific resistance problem) for 5 days or longer, recommended treatment is:

- **cefepime 50 mg/kg (max 2 g) IV, 8-hourly OR**
- **piperacillin+tazobactam 100 + 12.5 mg/kg (max 4 + 0.5 g) IV, 8-hourly OR**
- **ticarcillin+clavulanate 50 + 1.7 mg/kg (max 3 + 0.1 g) IV, 6-hourly**

Combination therapy using an aminoglycoside has shown a strong trend to reduced mortality for hospital-acquired pneumonia due to MDR organisms in critically ill adult patients. In children with severe pneumonia, consider adding to the above regimen:

- **gentamicin <10 years: 7.5 mg/kg; ≥10 years: 6 mg/kg IV, daily**

If Gram-positive cocci are seen on Gram stain and/or the hospital has a high prevalence of MRSA, add vancomycin to the above regimen, and discontinue it if cultures are negative after 48 hours:

- **vancomycin <12 years: 30 mg/kg (max 1 g) IV, 12-hourly, 12 years or older: 25 mg/kg (max 1 g) IV, 12-hourly**

Carbapenems should be reserved for children with organisms resistant to all other antibiotics. If indicated by susceptibility testing, recommended treatment is:

- **meropenem 25 mg/kg (max 1 g) IV, 8-hourly OR**
- **imipenem-cilastatin 25 mg/kg (max 1 g) IV, 6-hourly**

**Pneumonia in the immunocompromised child**

Children with underlying immunocompromise are at risk of infections with opportunist organisms. Children with defective humoral immunity (low antibodies) are most at risk of bacterial pneumonia with *S. pneumoniae* and untypeable *H. influenzae*. Children with defective cellular immunity (T cell) are at risk of *Pneumocystis carinii* (*P. jiroveci*) pneumonia (PCP) and infections with viruses such as CMV and fungi. Children with HIV infection or severe combined immunodeficiency may be susceptible to all the above organisms.

The type of immunodeficiency should be considered when deciding on treatment. Every attempt should be made to identify a causative organism. Induced sputum, bronchoscopy, fine needle aspiration, and/or open lung biopsy may be necessary to establish a specific diagnosis if examination of sputum or tracheal aspirates is unhelpful. The opinion of a clinical microbiologist or an infectious diseases physician should be sought.

**Pneumocystis jiroveci** (previously *Pneumocystis carinii*) pneumonia (PCP)

The classic presentation of PCP is with non-productive cough, fever, tachypnea, and dyspnea increasing in severity over a period of 2–3 weeks. Oxygen saturation is often low, but cyanosis is a late sign. Children can present, however, with a more fulminant presentation.

**Mild to moderate PCP**

Mild to moderate PCP is defined as PaO₂ >70 mm Hg in room air, alveolar–arterial gradient <35 mm Hg, and oxygen saturation >94% in room air. Recommended treatment is:

- **trimethoprim+sulfamethoxazole 5 + 25 mg/kg to 7 + 35 mg/kg orally, 8-hourly for 21 days**

If sulfamethoxazole is contraindicated, recommended treatment is:

- **dapsone 2 mg/kg (max 100 mg) orally, daily for 21 days PLUS**
- **trimethoprim 5 mg/kg (max 300 mg) orally, 8-hourly for 21 days**

**Severe PCP**

Severe disease is defined as PaO₂ <70 mm Hg in room air, alveolar–arterial gradient >35 mm Hg, and oxygen
saturation <94% in room air. Recommended treatment is:

**trimethoprim+sulfamethoxazole 5 + 25 mg/kg orally or IV, 6-hourly for a total of 21 days**

If allergic to trimethoprim+sulfamethoxazole, desensitization is recommended. If unresponsive to trimethoprim+sulfamethoxazole, recommended treatment is:

**pentamidine 4 mg/kg (max 300 mg) IV, daily for 21 days**

**Corticosteroids for PCP**

A Cochrane review of six studies of adults with PCP complicating HIV infection showed that giving corticosteroids in addition to antibiotics reduces the need for mechanical ventilation and saves lives. Improved survival with corticosteroid adjunctive therapy has been confirmed in two RCTs in children. As adjunctive therapy for PCP, we recommend:

**methylprednisolone 1 mg/kg (max 40 mg) IV, 6–12-hourly**

**Fungal pneumonia**

Fungi are often cultured from sputum, which usually represents colonization. In the immunocompromised patient with pneumonia, however, sputum fungal cultures may represent true infection, although the presence of deep fungal infection should be confirmed by bronchoalveolar lavage or biopsy. For the treatment of fungal pneumonia, specialist advice is essential. Duration of treatment is dictated by clinical response and resolution of the immunosuppression. A Cochrane review found that lipid-soluble amphotericin preparations tended to be more effective than conventional amphotericin for invasive fungal infection, although this did not reach statistical significance, and there was a non-significant trend toward improved mortality with lipid-soluble preparations. They also caused less nephrotoxicity, but are far more expensive.

**Aspergillus and lung disease**

**Question** For children with pulmonary Aspergillus infection, are azoles more effective than amphotericin B?

**Literature review** We found three RCTs, a non-Cochrane meta-analysis, and a Cochrane review of use of azoles in bronchopulmonary aspergillosis in asthma. We found no RCTs comparing azoles with amphotericin B for pulmonary aspergillosis. We found one large RCT of voriconazole versus amphotericin B for invasive aspergillosis, and a Cochrane review. We found one RCT comparing conventional amphotericin B with amphotericin B colloidal dispersion for invasive aspergillosis.

**Allergic bronchopulmonary aspergillosis**

In asthmatic children and children with cystic fibrosis, finding *Aspergillus* in the sputum in association with pulmonary infiltrates, raised serum IgE and/or IgG precipitins to *Aspergillus* species, is referred to as allergic bronchopulmonary aspergillosis. This condition is thought to be primarily an inflammatory condition and is managed with corticosteroids, with or without antifungals. A Cochrane review found only three RCTs of azoles in bronchopulmonary aspergillosis, two of them involving itraconazole and one ketoconazole. Voriconazole has not been studied in this setting. Itraconazole was found to modify the immunologic activation associated with allergic bronchopulmonary aspergillosis (reduced eosinophilia and IgE) and improved clinical outcome, at least over a period of 16 weeks. Improvement in lung function has not been shown. In one trial, the number of exacerbations requiring oral corticosteroids was increased with itraconazole, and there is potential concern about adrenal suppression when using inhaled steroids with itraconazole.

Recommended treatment for bronchopulmonary aspergillosis, in addition to corticosteroids, is:

**itraconazole 5 mg/kg (max 200 mg) orally, 12-hourly**

**Invasive pulmonary aspergillosis**

Invasive pulmonary aspergillosis occurs most often in immunocompromised children with prolonged severe neutropenia, is usually rapidly progressive, and requires systemic antifungal treatment. An RCT compared voriconazole with conventional amphotericin B for confirmed and presumed invasive *Aspergillus* infections in 391 patients 12 years or older with mainly hematologic malignancies or stem cell transplants. The study authors reported that voriconazole had significant benefit at 12 weeks, in terms of response to
therapy and mortality. A Cochrane review commented, however, that conventional amphotericin B was used without adequate attention to reducing its adverse effects by premedication and hydration. This resulted in a marked difference in the duration of treatment on trial drugs (77 days with voriconazole versus 10 days with amphotericin B), and they felt precluded meaningful comparisons of the benefits and harms of the two drugs.

Liposomal preparations of amphotericin have not been shown to be more effective than conventional amphotericin B for invasive aspergillosis. An RCT found that amphotericin B colloidal dispersion was as effective as conventional amphotericin B and less toxic. Recommended treatment for pulmonary aspergillosis is:

- voriconazole 6 mg/kg IV, 12-hourly for two doses, then 4 mg/kg IV, 12-hourly for at least 7 days, then 4 mg/kg up to 200 mg orally, 12-hourly OR liposomal amphotericin 3–5 mg/kg IV, daily OR amphotericin B desoxycholate 1 mg/kg IV, daily

Caspofungin, a recently introduced drug with activity against both Candida and Aspergillus, is very expensive. There are no RCTs of caspofungin in invasive aspergillosis. A retrospective study suggested that salvage treatment with caspofungin plus voriconazole may be superior to voriconazole alone for patients with invasive aspergillosis not responding to an amphotericin B-based regimen. We do not recommend using caspofungin except for salvage therapy and after expert advice from a microbiologist or infectious diseases physician.

**Candida pneumonia**

**Question** | For children with pulmonary candidiasis, is therapy with an azole as effective as amphotericin B or as caspofungin?

**Literature review** | We found 10 RCTs comparing azoles or caspofungin with amphotericin B treatment of candidiasis in non-neutropenic patients, and 1 non-Cochrane meta-analysis in adults. Isolation of Candida species from the respiratory tract is seldom of significance, as this organism frequently colonizes the respiratory tract, particularly of neonates and older children ventilated in intensive care units. A definitive diagnosis of candidal pneumonia rests on histologic evidence of fungal invasion of lung tissue, as well as radiologic changes.

For proven candidiasis, a non-Cochrane meta-analysis showed fluconazole is as effective as conventional amphotericin B and less toxic. The combination of fluconazole and amphotericin has not been shown to be superior to fluconazole alone. Conventional amphotericin B has not been shown to be inferior in efficacy to caspofungin or liposomal amphotericin, which are much more expensive, although liposomal amphotericin may be preferred to conventional amphotericin if the child has significant renal toxicity. Voriconazole is as effective as giving amphotericin B followed by fluconazole, but has not been shown to be superior to fluconazole, and is far more expensive. Prior fluconazole therapy is a risk factor for fluconazole-resistant candidiasis, so amphotericin B is preferred for children who have previously received fluconazole.

For fluconazole-naïve children, we recommend:

- **fluconazole 6 mg/kg IV, daily**

For children with fluconazole-resistant Candida and children who have already received fluconazole, if they are at low risk for renal impairment, we recommend:

- **amphotericin 1 mg/kg IV, daily**

For such children, if they have preexisting renal impairment or at high risk of developing it, we recommend:

- **liposomal amphotericin 3 mg/kg IV, daily OR voriconazole 6 mg/kg IV, 12-hourly for two doses, then 4 mg/kg 12-hourly**

[*It is recommended that voriconazole levels be monitored.*]

**Cryptococcus pneumonia**

Cryptococcus neoformans may cause primary community-acquired pneumonia with single or multiple pulmonary nodules in the normal host and in patients with defects in cellular immunity. The serum cryptococcal antigen is usually positive and the organism can sometimes be cultured from respiratory tract specimens. Recommended treatment is:

- amphotericin B desoxycholate 1 mg/kg IV, daily for 2–4 weeks **WITH OR WITHOUT**
flucytosine 25 mg/kg IV or orally, 6-hourly for 2 weeks
Alternatively, or for continuation after amphotericin, use:
flucytosole 12 mg/kg (max 800 mg) orally or IV
as a single dose, then 24 hours later, 6 mg/kg
(max 400 mg) orally, daily for at least 4 weeks of therapy

Aspiration pneumonia
Aspiration pneumonia often involves anaerobes such as Bacteroides fragilis or mouth flora such as S. miller. There are few antibiotic trials. Clindamycin and penicillin are equivalent in efficacy in children. S. aureus infection is rare in aspiration and is adequately treated by clindamycin, which is also recommended if there is penicillin allergy. If aspiration has resulted in a lung abscess, treat as for lung abscess, below. For empiric treatment of aspiration pneumonia, recommended treatment is:

clindamycin 10 mg/kg (max 450 mg) IV or orally,
8-hourly OR the combination of
benzylpenicillin 30 mg (50,000 U)/kg (max 1.2 g
or 2 million U) IV, 6-hourly PLUS
metronidazole 12.5 mg/kg (max 500 mg) IV,
12-hourly OR 10 mg/kg (max 400 mg) orally,
12-hourly

We recommend adding a third-generation cephalosporin if Gram-negative bacilli are found in the sputum or Gram-negative pneumonia is suspected. In adults, ampicillin+ sulbactam is as effective as clindamycin+ cephalosporin.

When the child has improved, we recommend switching to oral therapy:

clindamycin 10 mg/kg (max 450 mg) orally,
8-hourly OR
amoxicillin + clavulanate 22.5 + 3.2 mg/kg (max
875 + 125 mg) orally, 12-hourly

For uncomplicated aspiration pneumonia, a total of 7 days of therapy is usually adequate.

Lung abscess
Lung abscess in children is most commonly a complication of dental sepsis but can occur secondary to aspiration or as a complication of severe, necrotizing pneumonia. Patients with altered conscious states (e.g., from anesthesia or postictal) and/or with swallowing difficulties are at increased risk. Septic emboli are occasionally a cause in patients with right-sided endocarditis. Rarely, lung abscesses can occur as a complication of septic thrombophlebitis of the internal jugular vein (Lemierre syndrome). It is not unusual to find no obvious cause of a lung abscess. The usual organisms are mouth flora, such as S. milleri and anaerobes.

If the cause is necrotizing pneumonia, pathogens such as S. aureus (see p. 188) and Klebsiella pneumoniae should be considered.

Whenever possible, an attempt should be made to identify the causal organism, using bronchoscopy, or surgical or interventional radiology techniques such as guided fine needle aspiration to obtain diagnostic specimens.

Clindamycin was superior in a small trial in adults. For empiric antibiotic therapy, we recommend:

clindamycin 10 mg/kg (max 450 mg) IV or orally,
8-hourly OR the combination of
benzylpenicillin 30 mg (50,000 U)/kg (max 1.2 g
or 2 million U) IV, 6-hourly PLUS
metronidazole 12.5 mg/kg (max 500 mg) IV,
12-hourly OR 10 mg/kg (max 400 mg) orally,
12-hourly

We recommend adding a third-generation cephalosporin if Gram-negative bacilli are found in the sputum or Gram-negative pneumonia is suspected. In adults, ampicillin+ sulbactam is as effective as clindamycin+ cephalosporin.

Antibiotic therapy is generally required for at least 10–14 days, but we recommend continuing until any sputum is no longer purulent and the abscess cavity is free of fluid (in some cases this may require up to 4 weeks of treatment).

Pleural empyema
Parapneumonic effusions can be pyogenic (empyemas), can be due to other organisms such as M. pneumoniae or M. tuberculosis, or may have noninfectious causes. Pleural empyema affects nearly 1 of every 150 children hospitalized with pneumonia. Pleural empyema is usually secondary to acute bacterial pneumonia, although may also result from
hematogenous spread. The causative organisms are the same as for pneumonia, but the frequency is different. In a large retrospective US series, the commonest organisms were S. aureus (35%), S. pneumoniae (30%), and S. pyogenes (20%). Un-typeable H. influenzae is also represented in many series, while H. influenzae type b is an important cause in unimmunized populations. M. pneumoniae can cause small to moderate pleural effusions.

Diagnosis of pleural empyema

**Question** | In a child with pleural effusion, are pleural fluid parameters reliable for diagnosing empyema?

**Literature review** | We found seven studies comparing pleural fluid pH, lactate dehydrogenase (LDH) and glucose, and a meta-analysis.

Thoracocentesis is almost always indicated in suspected pleural empyema to make the diagnosis and because the Gram stain and culture results guide specific therapy while the consistency of the pleural fluid may help in decisions about surgery.

Analysis of the pleural fluid pH, LDH, and glucose levels in parapneumonic effusions is potentially useful in diagnosing empyema and guiding decisions on the need for drainage. A meta-analysis of seven studies reporting values for pleural fluid pH, LDH, or glucose used area under the ROC curve (AUC) as a measure of sensitivity and specificity. Pleural fluid pH had the highest diagnostic accuracy for all patients with parapneumonic effusions (AUC = 0.92) compared with pleural fluid glucose (AUC = 0.84) or LDH (AUC = 0.82). After excluding patients with purulent effusions, pH (AUC = 0.89) retained the highest diagnostic accuracy. Pleural fluid pH decision thresholds varied between 7.21 and 7.29 depending on cost-prevalence considerations.

Antibiotic treatment of pleural empyema

In the only RCT of antibiotic treatment for pleural empyema, cefuroxime was equivalent to dicloxacillin+ chloramphenicol.

For empiric antibiotic treatment, we recommend:

- **cefuroxime 50 mg/kg (max 2 g) IV, 8-hourly** OR
- **cefotaxime 50 mg/kg (max 2 g) IV, 8-hourly**

When cMRSA is suspected, e.g., because child from ethnic group with high incidence, we recommend adding to the above treatment:

- **clindamycin 10 mg/kg (max 450 mg) IV, 8-hourly**

For patients with anaphylactic penicillin allergy and severely ill patients, until antibiotic susceptibility data are available, recommended treatment is:

- **vancomycin <12 years: 30 mg/kg (max 1 g) IV, 12-hourly, 12 years or older: 25 mg/kg (max 1 g) IV, 12-hourly PLUS**
- **cefotaxime 50 mg/kg (max 2 g) IV, 8-hourly**

Operative therapy for pleural empyema

**Question** | For children with pleural empyema, does primary surgical treatment compared with primary non-operative therapy (antibiotics and thoracentesis/chest tube drainage) speed recovery?

**Literature review** | We found 67 studies of operative or non-operative management of pediatric empyema, 8 studies comparing the two, a non-Cochrane meta-analysis but only 1 RCT and a Cochrane review.

The evidence regarding immediate surgical versus non-surgical intervention for empyema is weak. A non-Cochrane meta-analysis found 67 observational studies, but children were not randomized to operative or non-operative management in any study. Data were aggregated from reports of children initially treated non-operatively (3418 cases from 54 studies) and of children treated with a primary operative approach (363 cases from 25 studies). The primary operative group had a lower aggregate in-hospital mortality rate (0% versus 3.3%), reintervention rate (2.5% versus 23.5%), length of stay (10.8 days versus 20.0 days), duration of tube thoracostomy (4.4 days versus 10.6 days), and duration of antibiotic therapy (12.8 days versus 21.3 days), compared with patients who underwent non-operative therapy. Although these results look impressive, it should be remembered that non-randomized studies are prone to selection bias.

A Cochrane review found only one RCT. In this study, 20 adults with empyema that was loculated or had pH < 7.2 were randomized to immediate surgery using video-assisted thoracoscopic surgery or to chest tube drainage combined with streptokinase. The
surgical group had a significantly higher primary treatment success, shorter chest tube duration (5.8 days versus 9.8 days), and shorter hospital stay (8.7 days versus 12.8 days).

The limited data seem to favor immediate surgery for large empyemas.

**Fibrinolytic therapy for pleural empyema**
A meta-analysis of three small RCTs (total 104 patients) comparing fibrinolytic therapy with streptokinase or urokinase against saline favored fibrinolytic therapy, but results were not always consistent. A subsequent large RCT of 454 patients found that intrapleural streptokinase had no benefit over placebo and was associated with an increase in serious adverse events.

**Prevention of pleural empyema**
Two non-Cochrane meta-analyses suggest that prophylactic antibiotics are indicated to reduce the risk of empyema in patients with chest drains inserted for trauma. The antibiotics used should cover S. aureus.

**Bronchiectasis**
Bronchiectasis is irreversible dilatation of the subsegmental airways, causing chronic, recurrent cough, and sputum production. Bronchiectasis may follow severe childhood pneumonia, and its incidence has fallen in industrialized countries, as measles, pertussis, and tuberculosis have become rare. Nevertheless, bronchiectasis may rarely result from severe pneumonia due to adenovirus or other viruses. Bronchiectasis remains more common in developing countries and in some indigenous groups in industrialized countries. There are diseases in which bronchiectasis may occur as a result of failure to clear the airways due to increased viscosity of secretions as in cystic fibrosis (see below), reduced ciliary activity (ciliary dysmotility syndromes), or defective immunity. These need to be excluded.

In non-CF bronchiectasis, the commonest organisms isolated from sputum are untypeable H. influenzae, S. pneumoniae, and P. aeruginosa. Physiotherapy and intermittent courses of oral or inhaled antibiotics for exacerbations are often recommended.

**Antibiotics for bronchiectasis**

**Question** | In children with bronchiectasis not due to cystic fibrosis, do prolonged antibiotics compared with no antibiotics or placebo improve outcome?

**Literature review** | We found six RCTs on prolonged antibiotic treatment of non-cystic fibrosis (non-CF) bronchiectasis and a Cochrane review.

A Cochrane review of six studies of antibiotics used for 4 weeks to 1 year showed that prolonged antibiotics had significant clinical benefit in terms of response to treatment, but they did not decrease the number of exacerbations. The review was limited by the diversity of the trials. An individual decision for each patient will be needed regarding the benefits versus risks of long-term oral antibiotics. If used, the choice of antibiotic therapy should reflect the sensitivities of organisms isolated from sputum cultures. Studies of inhaled antibiotics have mostly been of tobramycin for non-CF patients colonized with *Pseudomonas*. They suggest an effect in reducing the density of sputum colonization, but with little demonstrable effect on patient’s well-being or lung function.

**Physical therapy for bronchiectasis**
Although physiotherapy is always recommended, the evidence for its efficacy in non-CF bronchiectasis is scanty. We found eight RCTs on physical therapy, but most studies were in adults. There is, however, good evidence of short-term benefit in cystic fibrosis, and it seems reasonable to extrapolate this to non-CF bronchiectasis. If physiotherapy is used, a Flutter device is preferred to percussion or active breathing techniques. Exercise training improves lung function in bronchiectasis and should be encouraged.

**Cystic fibrosis**

**Antibiotics for cystic fibrosis**

**Infants**

**Question** | In infants with cystic fibrosis, do prophylactic antistaphylococcal antibiotics compared with no antibiotics or placebo improve outcome?

**Literature review** | We found four RCTs on antistaphylococcal antibiotic use in infants and a Cochrane review.

We found no RCTs on prophylactic antistaphylococcal antibiotics. The Cochrane review found four RCTs on antistaphylococcal antibiotic use in infants and a fourth RCT comparing 2 antibiotics. These studies used different regimens, and the small number of infants in each study limits the certainty of their results. These studies suggest a benefit of prophylactic antibiotics, but due to the small number of infants in each study, the certainty of their results is limited.
It was traditionally taught that infants acquired *S. aureus* before they acquired *Pseudomonas* and that early antistaphylococcal therapy was beneficial. A Cochrane review of four studies involving 401 patients showed that prophylactic antistaphylococcal therapy can delay colonization with *S. aureus*, but the clinical benefits were uncertain.\(^\text{184}\) In addition, there was a trend toward a lower cumulative isolation rate of *P. aeruginosa* in the prophylaxis group at 2 and 3 years but toward a higher rate from 4 to 6 years.\(^\text{184}\) On the basis of this evidence, some clinics recommend prophylactic antistaphylococcal antibiotics from diagnosis until 2 years of age, and others recommend antibiotic treatment only if the child develops a moist cough, whether or not chest examination is normal. It is often not possible to get a microbiologic diagnosis because of difficulties in obtaining an adequate sputum sample from infants. If no sample is available, to treat both *S. aureus* and *H. influenzae*, we recommend amoxicillin + clavulanate 22.5 + 3.2 mg/kg orally, 12-hourly.

To treat *S. aureus* alone, use:

di/fluc/oxa/nafcillin 12.5 mg/kg orally, 6-hourly

If the moist cough persists despite the above treatment, consider admission for intravenous antibiotics.

**Initial *Pseudomonas* colonization**

**Question** | In children with cystic fibrosis who become newly colonized with *Pseudomonas*, does early antibiotic treatment compared with no antibiotic or placebo reduce long-term colonization?

**Literature review** | We found three studies of early antibiotic treatment of patients newly colonized with *Pseudomonas aeruginosa* and a Cochrane review.\(^\text{185}\)

There is limited evidence that early antibiotic treatment of patients newly colonized with *Pseudomonas aeruginosa* can reduce the proportion that become chronically colonized. A Cochrane review found 15 studies but only three RCTs (69 participants) of people with cystic fibrosis recently colonized with *P. aeruginosa* and comparing combinations of inhaled, oral, or intravenous antibiotics with placebo or usual treatment (or both) or other combinations of inhaled, oral, or intravenous antibiotics. There was evidence from two RCTs reported to be of questionable methodologic quality that treatment of early *P. aeruginosa* infection with inhaled tobramycin results in microbiologic eradication of the organism from respiratory secretions more often than placebo and that this effect may persist for up to 12 months.\(^\text{185}\) One small RCT of oral ciprofloxacin and nebulized colistin versus usual treatment suggested that treatment of early infection results in microbiologic eradication of *P. aeruginosa* more often than usual treatment after 2 years (RR 0.24, 95% CI 0.06–0.96). There is insufficient evidence to determine whether antibiotic strategies for the eradication of early *P. aeruginosa* decrease mortality or morbidity, improve quality of life, or are associated with adverse effects compared to placebo or standard treatment.

Because avoiding chronic *Pseudomonas* colonization is important and the risks of short-term antibiotics are very low, we recommend that antibiotics active against *Pseudomonas* be given when patients become newly colonized with *P. aeruginosa* and repeated with each early recurrence in an attempt to prevent chronic colonization. The choice of antibiotic should ideally be based on susceptibility testing, but if not yet available, recommended empiric therapy:

ciprofloxacin 10 mg/kg (max 500 mg) orally, 12-hourly for 3 weeks PLUS EITHER tobramycin: child <5 years: 40 mg by inhalation, 12-hourly; child 5–10 years: 80 mg, 12-hourly; >10 years and adult: 160 mg, 12-hourly OR gentamicin: child <5 years: 40 mg by inhalation, 12-hourly; child 5–10 years: 80 mg, 12-hourly; >10 years and adult: 160 mg, 12-hourly

[NB: Single doses, not per kilogram. Dilute 40 and 80 mg doses of tobramycin or gentamicin to 4 mL with 0.9% saline.]

The antibiotics should be changed if the *Pseudomonas* is found to be resistant. If colonization and respiratory symptoms persist despite the above treatment, consider admission for intravenous antipseudomonal antibiotics.

**Elective admission (“tune-ups”) for cystic fibrosis**

Some cystic fibrosis clinics bring children into hospital on a regular basis even when well for physiotherapy and antibiotics. These elective admissions are sometimes called “tune ups.”
**Question** | In children with cystic fibrosis, do regular elective admissions compared with treating children only when symptomatic improve outcome?

**Literature review** | We found three studies and a Cochrane review.\(^{187}\)

A Cochrane review included only two studies (79 participants) in the review.\(^{187}\) Differences in study design and objectives meant that data could not be pooled for meta-analysis. Neither study demonstrated significant differences in outcome measures between intervention and comparison groups. We conclude that the evidence for regular elective admissions is weak.

**Nebulized antibiotics for cystic fibrosis**

**Question** | In children with cystic fibrosis, does intermittent or long-term treatment with nebulized antibiotics compared to no treatment or placebo improve outcome?

**Literature review** | We found 14 RCTs, 2 non-Cochrane meta-analyses,\(^{186,189}\) and a Cochrane review.\(^{190}\)

A Cochrane review found 14 eligible trials (1100 participants) and 13 (985 participants) compared a nebulized antipseudomonal antibiotic with placebo or usual treatment.\(^{190}\) Tobramycin was studied in 8 trials. Follow-up ranged from 1 to 32 months. Lung function measured as forced expired volume in 1 second (FEV\(_1\)) was better in the treated group than in control group in nine studies. Resistance to antibiotics increased more in the antibiotic-treated group than in placebo group. Tinnitus and voice alteration were more frequent with tobramycin than placebo. The authors conclude that nebulized antipseudomonal antibiotics improve lung function, but more evidence is needed to determine if this benefit is maintained as well as to determine the significance of development of antibiotic-resistant organisms.\(^{190}\)

In the USA, the usual adolescent or adult dose of tobramycin is 300 mg, but lower doses are often used elsewhere. If it is decided to use nebulized antibiotics, we recommend:

\[
\text{tobramycin <5 years: 40 mg, 5–10 years: 80 mg, >10 years: 160 mg, nebulized, 12-hourly}
\]

[\(\text{NB: Single doses, not per kilogram. Dilute 40 and 80 mg doses to 4 mL with 0.9% saline.}\)]

**OR**

\[
\text{gentamicin <5 years: 40 mg, 5–10 years: 80 mg, >10 years: 160 mg, nebulized, 12-hourly}
\]

[\(\text{NB: Single doses, not per kilogram. Dilute 40 and 80 mg doses to 4 mL with 0.9% saline.}\)]

**Exacerbations in children with cystic fibrosis colonized with Pseudomonas**

Treatment of exacerbations of colonized children with antipseudomonal antibiotics should be based on sensitivities. Duration should depend on clinical response, but 10–14 days of treatment is often used. The antibiotics may be given orally (ciprofloxacin), nebulized, or intravenously, or a combination of these. It should be noted that cefotaxime and ceftriaxone have no useful activity against *Pseudomonas* species. Ceftazidime and cefepime, on the other hand, have excellent antipseudomonal activity as long as organisms remain sensitive.

A Cochrane analysis showed no difference between single and combination intravenous antibiotics, but there was considerable heterogeneity of the 27 trials, and the authors felt the results were inconclusive.\(^{191}\) There is no evidence that combinations of inhaled and intravenous antibiotics are more effective, but they are often used. The optimum mode of delivery will depend on the child’s clinical situation. The choice of antibiotics should always depend on the sensitivities of the organisms cultured from sputum.

**Burkholderia cepacia**

In the 1980s, it was recognized that *B. cepacia* (previously called *P. cepacia*) was an opportunistic lung pathogen in cystic fibrosis and was associated with increased rates of morbidity and mortality.\(^{192–195}\) The clinical course of patients colonized with *B. cepacia* is variable, and it is not clear whether *B. cepacia* colonization causes deterioration or that patients do not become colonized until they are already deteriorating from other causes. We could find no RCTs of treatment of patients colonized with *B. cepacia*. *B. cepacia* is inherently resistant to many antibiotics, and treatment must be based on sensitivities.

**Macrolides**

Macrolides can modify host immune response and may have benefits in diseases where the host immune response contributes to pathology. A Cochrane review
found two studies, one in adults and one in children, suggesting that 6 months of oral azithromycin produced small but significant improvements in lung function.\textsuperscript{196} The authors of the Cochrane review argued against widespread use of azithromycin until further studies are available. Because azithromycin is expensive and long-term use will drive macrolide and possibly multidrug resistance, we think this is wise advice.

Physical therapy for cystic fibrosis
There is good evidence that physiotherapy provides short-term benefit in cystic fibrosis.\textsuperscript{181} A Flutter device is preferred to percussion or active breathing techniques.\textsuperscript{182} A Cochrane review of seven studies provided limited evidence that aerobic or anaerobic physical training improves exercise capacity, strength, and lung function.\textsuperscript{197}

Hypertonic saline for cystic fibrosis
A Cochrane review of 14 trials showed that nebulized hypertonic saline improves short-term mucociliary clearance and appears to increase lung function.\textsuperscript{198} Two subsequent RCTs of long-term nebulized hypertonic saline for 2 years showed improved mucus clearance, improved lung function, and fewer respiratory exacerbations.\textsuperscript{199,200} We found two published studies comparing hypertonic saline with recombinant deoxyribonuclease (rhDNase) in cystic fibrosis, and one abstract. In one study in children, hypertonic saline was not as effective as rhDNase, although there was variation in individual response. The mean FEV\textsubscript{1} increased by 16% with daily rhDNase, 14% with alternate-day rhDNase, and 3% with hypertonic saline.\textsuperscript{201} A crossover study comparing hypertonic saline with rhDNase found that both treatments improved lung function to the same extent.\textsuperscript{202} Hypertonic saline is considerably cheaper than rhDNase and appears to give comparable benefit, but is not always well tolerated in young children. We recommend a trial of therapy of hypertonic saline before using rhDNase.

rhDNase for cystic fibrosis
A Cochrane review of rhDNase in cystic fibrosis identified 14 eligible trials (2397 participants) and 3 additional studies that examined the health-care cost from one of the clinical trials.\textsuperscript{203} Eleven studies compared rhDNase to placebo, 1 compared daily rhDNase with hypertonic saline with hypertonic saline and alternate-day rhDNase\textsuperscript{201} and 2 compared daily rhDNase with hypertonic saline. Study duration varied from 6 days to 2 years. Lung function measured by spirometry improved in the treated groups, with significant differences at 1 month, 3 months, 6 months, and 2 years. There was no excess of adverse effects except voice alteration and rash. Insufficient data were available to analyze differences in antibiotic treatment, inpatient stay, and quality of life. On the other hand, hypertonic saline has not been clearly shown to be inferior to rhDNase; there is individual variation and saline is much cheaper.

We recommend a trial of therapy of hypertonic saline before using rhDNase.

Severe acute respiratory syndrome
Severe acute respiratory syndrome (SARS) is caused by the SARS-associated coronavirus and is primarily transmitted by respiratory droplet transmission.\textsuperscript{204} Some infected adults shed masses of virus, while most do not. The therapeutic use of nebulizers generated aerosols, which disseminated the organism and spread the disease. SARS is relatively mild in children, which suggests an important immunologic component to the pathogenesis of disease. At the time of writing, the last reported cases occurred in China in 2004. If SARS reemerges, precautions will need to be resumed. Strict infection control, respiratory and personal contact precautions are necessary to prevent person-to-person transmission. If SARS is suspected, the local health department must be notified. For information on SARS, readers are referred to the WHO Web site: http://www.who.int/csr/sars/en/ or the CDC Web site: http://www.cdc.gov/niosh/topics/SARS/.

Tuberculosis (TB)
TB often presents very differently in children from adults. In children, TB is usually the primary infection and is of very low infectivity to others, unless the child has military TB or adult-type open TB. The main differences are shown in Table 12.1.

Adults with pulmonary TB classically present with “open TB” with cavitating lesions. They are “smear positive” with acid-fast bacilli visible on sputum microscopy. In contrast, if children present with pulmonary TB (as opposed to being diagnosed on screening), it is usually with complications of hilar
Table 12.1 Differences between adult and pediatric pulmonary TB.

<table>
<thead>
<tr>
<th>Category</th>
<th>Adult</th>
<th>Child</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of infection</td>
<td>Reactivation</td>
<td>Primary</td>
</tr>
<tr>
<td>Organism load</td>
<td>Large</td>
<td>Small</td>
</tr>
<tr>
<td>Infectivity</td>
<td>High</td>
<td>Very low</td>
</tr>
<tr>
<td>Risk of miliary disease</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>

Adapted from Reference 205.

lymphadenopathy. The hilar nodes can compress the major bronchus causing wheeze or even hypostatic pneumonia, can rupture into the bronchus causing tuberculous pneumonia, or can rupture into the pleural cavity causing empyema.

An important distinction is drawn between TB infection and TB disease. Early after inhaling the organism, the patient is infected, but has not yet developed any clinical manifestations. A patient who remains well with no clinical disease is said to have TB infection; i.e., infection is latent. A patient who develops signs or symptoms has TB disease.

Diagnosis of TB
Because it is rare to see or culture *M. tuberculosis* in children (apart from adolescents with adult-type “open TB” cavitatory pulmonary disease), the diagnosis in children generally relies on demonstrating the host immune response to the organism. The classic method is using tuberculin skin testing (TST), although interferon-gamma assays are generating much interest.

TST and TB
TST is the traditional technique for distinguishing TB-infected from TB-uninfected persons from those who have TB infection or TB disease. False negatives can occur in very young babies, in children who are malnourished or immunocompromised extremely unwell with TB, e.g., with miliary disease. False positives can occur due to infection with cross-reacting non-tuberculous mycobacteria (see p. 202). Interpretation of TST requires consideration of prevalence and the purpose for testing.

A systematic review found that for the general US population, TST was sensitive and specific for diagnosing TB infection (latent infection) and 100% sensitive for diagnosing TB disease. The authors concluded that the operating characteristics of the tuberculin test are superior to those of nearly all commonly used screening and diagnostic tests.

Although the Red Book says to ignore previous BCG immunization in interpreting TSTs, a meta-analysis showed that the tuberculin skin response is more likely to be positive if the child has had BCG vaccine and the size of the response is likely to be increased up to 15 mm but not usually greater for 5 years or more after BCG. The Red Book Committee recommends giving chemoprophylaxis to asymptomatic children with a TST response of 10–14 mm, even if they had BCG. However, other authorities would not give chemoprophylaxis to a child who had received BCG unless the TST was 15 mm or greater (see Table 12.2), an approach that will reduce the number of children (particularly refugee children) given prophylaxis and seems logical on the basis of the evidence.

Table 12.2 Working definitions of positive TST.

<table>
<thead>
<tr>
<th>Induration</th>
<th>Tuberculin Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mm or greater</td>
<td>Child contact of person with infectious TB disease</td>
</tr>
<tr>
<td></td>
<td>Child thought to have TB disease</td>
</tr>
<tr>
<td></td>
<td>Immunosuppressed child, e.g., HIV, or on steroids or cytotoxics</td>
</tr>
<tr>
<td>10 mm or greater</td>
<td>Child &lt; 4 years old</td>
</tr>
<tr>
<td></td>
<td>Child any age with chronic disease, e.g., diabetes, malnutrition, renal failure</td>
</tr>
<tr>
<td></td>
<td>Child born (or parents born) in region with high prevalence of TB</td>
</tr>
<tr>
<td></td>
<td>Child who has traveled to region with high prevalence of TB</td>
</tr>
<tr>
<td></td>
<td>Child frequently exposed to adults at high risk of TB</td>
</tr>
<tr>
<td>15 mm or greater</td>
<td>Child &gt; 4 years old with no risk factors</td>
</tr>
<tr>
<td></td>
<td>Child who has received BCG vaccine in last 5 years</td>
</tr>
</tbody>
</table>

Respiratory infections
Interferon-gamma assays and TB
Until recently, TSTs were the only way to diagnose latent TB. In vitro tests have now been developed, based on the detection of interferon-gamma produced by T cells in response to TB infection. A systematic review of 75 studies suggested that the better interferon-gamma-based tests may have some advantages over TST, in terms of higher specificity, better correlation with exposure to M. tuberculosis, and less cross-reactivity due to BCG or non-tuberculous mycobacteria. On the other hand, they are expensive, and there is less evidence for children, for persons who are immunocompromised, who have extrapulmonary TB or non-tuberculous mycobacterial infection and in TB endemic countries. Because the interferon-gamma-based tests are not affected by prior BCG immunization they can be used in situations where the results of TSTs are likely to be confounded by prior BCG vaccination, e.g., contact tracing, immigrant screening, and surveillance programs.

Nucleic acid detection and TB
Because infection in children is pauci-bacterial, there is a need for highly sensitive tests to detect M. tuberculosis. The use of PCR techniques to amplify nucleic acid held great promise in TB, although the promise has not entirely been fulfilled. Although PCR can be useful, it is still not sensitive enough for a negative PCR to exclude infection. For example, according to a meta-analysis of 14 studies, the sensitivity of PCR of the CSF in diagnosing tuberculous meningitis is only 56%. The sensitivity and specificity of PCR is also not consistently good enough to recommend its routine use for smear-negative pulmonary TB. However, by sequencing the product, PCR techniques can distinguish between M. tuberculosis and atypical mycobacterial infection. In addition, by looking at gene mutations, PCR can be used to predict the sensitivity of an isolate of M. tuberculosis to antituberculous drugs.

Treatment of TB
Treatment of latent TB infection

Question In otherwise healthy children with latent TB infection, does chemoprophylaxis using one or more antituberculous drugs compared with no chemoprophylaxis or placebo reduce the risk of TB disease?

Literature review We found 11 RCTs of chemoprophylaxis and a Cochrane review.

Patients with latent TB infection (no signs or symptoms) may progress to develop active TB disease. Risk factors include young age, particularly children <4 years old, recent infection within the previous 2 years, and immunosuppression. A Cochrane review of 11 trials of non-HIV infected children showed that isoniazid chemoprophylaxis reduced the proportion of children and young adults with latent TB who progressed to active TB by 60% (95% CI 48–69%). There was no difference between 6 and 12 months of isoniazid, so although some authorities recommend 6 months of isoniazid and others recommend 9 months, there seems little evidence to support continuing for 9 months. Six months of rifampin (rifampicin) can be used as an alternative, e.g., for isoniazid-resistant TB, but there are fewer data on its efficacy.

After active TB has been excluded, children with a positive tuberculin skin test or TB-specific interferon-gamma release assay who should be considered for chemoprophylaxis are:

- young children (the risk of progression increases with decreasing age);
- children with HIV infection (long-term preventive therapy is protective, although the effect may decline with time);
- close contacts of a patient with smear-positive pulmonary TB;
- recent tuberculin converters;
- prior to the commencement of immunosuppressive therapy (including with corticosteroids or tumor necrosis factor inhibitors such as infliximab and etanercept);
- children with underlying medical conditions such as diabetes and chronic renal failure.

Recommended treatment is:

isoniazid 10 mg/kg (max 300 mg) orally, daily for 6 months

Supplemental pyridoxine is recommended for adults (25 mg) and for breast-fed babies (5 mg, if no syrup available can crush a 25-mg tablet, make up to 5 mL with water, and give 1 mL). The Red Book states that directly observed twice-weekly isoniazid for 9 months is an alternative if daily
therapy is not possible. This regimen lacks supportive data, but may be the only practical approach if compliance is a problem. Use:

isoniazid 15 mg/kg (max 900 mg) orally, twice-weekly for 9 months

Treatment of TB disease
M. tuberculosis is a slow-growing intracellular organism, and treatment for less than 6 months is associated with a lower success rate.218

Standard short-course therapy for 6 months is suitable to treat pulmonary TB and also cervical lymphadenitis due to TB,218 provided that:
· any organisms cultured are susceptible to isoniazid, rifampicin, and pyrazinamide;
· the patient is able to tolerate all drugs in the regimen;
· isoniazid and rifampicin are taken for the full 6 months and pyrazinamide for at least the first 2 months;
· cavitation is absent on the initial chest film and sputum cultures are negative after 2 months of treatment.

Standard short-course therapy is unsuitable if resistance to isoniazid or rifampicin is documented or is suspected on epidemiologic grounds, or if pyrazinamide cannot be used in the first 2 months. If standard short-course therapy is unsuitable, treatment for 9–12 months will be required.

Question | For children with TB disease, does intermittent therapy compared with daily therapy cure infection?

Literature review | We found 27 observational studies, 8 RCTs, and a Cochrane meta-analysis.219

A Cochrane meta-analysis219 considered only one trial comparing daily therapy with intermittent dosing220 to be eligible and thus concluded that there is insufficient evidence. Two RCTs in children, one in South Africa221 and one in India,222 found no difference in relapse rates between children treated with daily or intermittent dosing, but no difference in compliance.221

The weight of evidence from RCTs and from many observational studies suggests that intermittent dosing is associated with a low relapse rate comparable to daily dosing. Because of resource implications and to improve compliance, intermittent dosing regimens are often used. Daily therapy is sometimes preferred in children in industrialized countries but intermittent (thrice-weekly) regimens may be used for reasons of compliance and resources to treat older children. Intermittent regimens are recommended only if directly observed therapy (DOT) is available. Dosage should be reviewed if weight changes significantly during therapy.

Daily regimen
For the daily regimen, recommended treatment is:

isoniazid 10 mg/kg (max 300 mg) orally, daily for 6 months PLUS
rifampicin 10 mg/kg (max 600 mg) orally, daily for 6 months PLUS
pyrazinamide 25 mg/kg (max 2 g) orally, daily for 2 months

Because of concerns about its effect on vision, ethambutol is not recommended for children <6 years old. If used instead of or as well as pyrazinamide, the dose of ethambutol is 15 mg/kg daily for 2 months, but stop earlier if the organism is shown to be sensitive to isoniazid and rifampicin.

Thrice-weekly regimen (with DOT)
For the thrice-weekly regimen, recommended treatment is:

isoniazid 15 mg/kg (max 600 mg) orally, thrice weekly for 6 months PLUS
rifampicin 15 mg/kg (max 600 mg) orally, thrice weekly for 6 months PLUS
pyrazinamide 50 mg/kg (max 3 g) orally, thrice weekly for 2 months

Because of concerns about its effect on vision, ethambutol is not recommended for children <6 years old. If used instead of or as well as pyrazinamide, the dose of ethambutol is 30 mg/kg thrice weekly for 2 months, but stop earlier if the organism is shown to be sensitive to isoniazid and rifampicin.

Extrapulmonary TB
Although there are few formal studies of duration of therapy, it is recommended that children with most forms of extrapulmonary TB, e.g., lymph node,223 bone, pleural, can be treated with standard short-course therapy for 6 months.207 Patients with miliary (disseminated) and CNS TB (tuberculous meningitis, tuberculoma, TB spine) should be treated for
12 months (2 months with three or four drugs, followed by 10 months of rifampicin and isoniazid). Prolongation of therapy should be considered for any child with TB that has not resolved after 6 months.207

**Corticosteroids**

Corticosteroids reduce mortality and severe residual disability in tuberculous meningitis in children.224 They are also often used for children with tuberculous pleurisy,225 endobronchial obstruction, pericardial effusion, and severe miliary TB, but there is no good evidence for or against these indications.

The usual dose is prednisone 1–2 mg/day up to 60 mg daily for 6–8 weeks (expert opinion), although some authors have recommended higher doses for theoretical reasons but without evidence that the benefits exceed the likely harms.

**Directly observed therapy**

The WHO and others have stressed the importance of DOT to improve compliance and reduce the risk of inducing resistance. A Cochrane meta-analysis was unable to show any significant benefit of DOT above self-treatment at home.226 However, the six studies reviewed excluded patients at high risk of non-compliance. For the same reasons as the WHO, we still strongly advise using DOT whenever resources permit.

**TB in pregnancy and breast-feeding**

A pregnant woman with suspected TB should be treated with antituberculous medication urgently, because of the high risk of TB to the fetus. Isoniazid, rifampicin, and ethambutol all cross the placenta, but have not been reported to be teratogenic. Although US guidelines state that pyrazinamide is not recommended for routine use in pregnant women because of insufficient safety data, pyrazinamide is widely used in this situation in other countries.

Breast-feeding is considered to be safe for women who are being treated with isoniazid, rifampicin, and ethambutol because the low concentrations of these drugs in breast milk have not been shown to be toxic for the nursing infant. However, to prevent deficieny, it is recommended to give pyridoxine 5 mg on the days that the mother receives her isoniazid dose to babies who are being breast-fed by mothers who are taking isoniazid (with or without pyridoxine).

**Prevention of TB**

In a meta-analysis of RCTs, BCG vaccine given to newborns or infants was 74% effective against TB disease, 65% protective against death, and 64% against TB meningitis.227 Better studies reported greater efficacy. Although the efficacy of BCG vaccine wanes with time,228 we have no better vaccine at present. BCG is a live, attenuated vaccine (*M. bovis*) and is contraindicated for highly immunocompromised children.

**Non-tuberculous mycobacterial infection**

Non-tuberculous mycobacteria are environmental organisms, which can cause respiratory, cutaneous, or disseminated disease. Isolation of these organisms from respiratory secretions does not distinguish between colonization and infection. Defense to these organisms depends on T-cell function and in particular on interferon-gamma activity.

**Question** | For children with non-tuberculous mycobacterial infections, does treatment with three antimycobacterial drugs compared with two drugs cure infection?

**Literature review** | We found 48 studies and 2 RCTs in HIV-infected adults, and 1 RCT in HIV-negative adults.234

The evidence on optimal treatment of non-tuberculous mycobacterial infections is weak. We could find only two RCTs comparing three drugs, with two drugs in HIV-infected adults and one in HIV-negative adults.234 These favored three-drug regimens, although the evidence was stronger in HIV-infected than HIV-negative patients.

**Mycobacterium avium complex (MAC)**

MAC can cause:

- cervical lymphadenitis, which is usually treated surgically;
- pulmonary MAC;
- disseminated MAC, which occurs in immunocompromised patients with impaired T-cell immunity, e.g., severe combined immunodeficiency, HIV, or in association with familial defects in the interferon-gamma receptor.229–231

For most drugs, with the exception of clarithromycin and azithromycin, there is poor correlation between
in vitro susceptibility testing and clinical response to
treatment of MAC.

The following recommendations are based largely
on expert consensus opinion.235–237

For pulmonary MAC, a combination of three drugs
is recommended.235–237 Daily therapy is more effective
than thrice-weekly regimens in severe cases.236 Treatment
duration (with all three drugs) depends on clinical,
microbiological, and radiological responses, but
should continue until the patient has been culture-
negative for at least 12 months.

For the daily regimen, we recommend:

- **isoniazid 10 mg/kg (max 300 mg) orally, daily**
- **rifamp(ic)in 10 mg/kg (max 600 mg) orally, daily**
- **ethambutol child ≥6 years: 15 mg/kg orally, daily**

 Recommended treatment duration is 18 months, with
at least 12 months of negative sputum cultures.

**References**


34 Hammaren-Malmi S, Saxen H, Tarkkanen J, Mattila PS. Adenoidectomy does not significantly reduce the incidence of otitis media in conjunction with the insertion of tympanostomy tubes in children who are younger than 4 years: a randomized trial. *Pediatrics* 2005;116:185–9.


44 Rovers MM, Black N, Browning GG, Maw R, Zielhuis GA, Haggard MP. Grommets in otitis media with effusion:
50 Macfadyen CA, Acuin JM, Gamble C. Systemic antibiotics versus topical treatments for chronically discharging ears with underlying eardrum perforations. The Cochrane Database of Systematic Reviews 2006;(1)Art No CD005608.


147. Wark PAB, Hensley MJ, Saltos N et al. Itraconazole reduces eosinophilic airway inflammation in allergic


178 Evans DJ, Bara AI, Greenstone M. Prolonged antibiotics for purulent bronchiectasis. The Cochrane Database of Systematic Reviews 2003;(4):Art No CD001392.


van der Schans C, Prasad A, Main E. Chest physiotherapy compared to no chest physiotherapy for cystic fibrosis. The Cochrane Database of Systematic Reviews 2000;(2):Art No CD001401.


Southern KW, Barker PM, Solis A. Macrolide antibiotics for cystic fibrosis. The Cochrane Database of Systematic Reviews 2003;(3):Art No CD00203.


Wark PAB, McDonald V, Jones AP. Nebulised hypertonic saline for cystic fibrosis. The Cochrane Database of Systematic Reviews 2005;(3):Art No CD001506.


CHAPTER 13
Sexually transmitted and genital infections

13.1 Balanitis and balanoposthitis

Balanitis (inflammation of the glans penis), with or without posthitis (inflammation of the prepuce), is reported in 6% of uncircumcised and 3% of circumcised males.¹ Most cases are mild and recover without specific treatment. *Streptococcus pyogenes* is the most commonly reported organism cultured from skin swabs taken when the foreskin is retracted.² Infection causes pain, redness, and swelling, and may be associated with perianal cellulitis or other manifestations of group A streptococcal infection such as sore throat, rash, and fever. Toxic shock syndrome was reported in association with one case of staphylococcal balanitis.³ In adults, bacterial causes are less common than *Candida albicans*.

If *S. pyogenes* is cultured, use:

**phenoxyemethylpenicillin 10 mg/kg (max 500 mg) orally, 6-hourly**

Candidal balanitis occurs typically in sexually active, uncircumcised males, causing itchy, red, maculopapular lesions of the glans, with circumferential scale and satellite lesions. A combination of a topical antifungal and hydrocortisone is usually effective.

13.2 Vulvovaginitis

Vulvitis is local irritation of the vulva, and vaginitis is erythema and inflammation of the vaginal mucosa, usually with a vaginal discharge.⁴ Vulvovaginitis is common in prepupal girls⁴ and presents with redness, local irritation, dysuria, and often vaginal discharge. It is often stated that poor hygiene is a cause of vulvovaginitis, and in one study, poor hygiene and pinworms were the major reported cause.⁵ The lack of a control group casts doubt on this claim, and controlled studies have not found any increase in poor hygiene in patients compared with controls.⁶,⁷ Similarly, although bubble baths are often blamed,⁸ they were used more commonly by controls than patients in one controlled study.⁶ These examples illustrate the importance of including a control group before talking of associations as being risk factors for a disease or causes of the disease.

Potentially pathogenic organisms can be grown often from the vagina of girls with vulvovaginitis, and are blamed often.⁸,⁹ Culturing organisms does not mean they are causing the problem, however, since normal girls can carry most of the same organisms.⁶,⁷ When a controlled study was performed, potential pathogens were no more common in girls with vulvovaginitis than in controls.⁶ One uncontrolled study found *S. pyogenes* in cultures from 21% of girls with vulvovaginitis.⁹

A number of associations with and possible causes of vulvovaginitis are given in Box 13.1.

Non-specific vulvovaginitis

We recommend that non-specific vulvovaginitis, with no cause found, should not be treated with specific agents, but only symptomatically. In a study of 50 girls

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Box 13.1 Causes of vulvovaginitis.

- Non-specific
- Worms
- Foreign body
- Group A streptococcus
- Group B streptococcus
- Gonorrhoea
- Chlamydia
- Candidiasis
- Trichomonas
- Bacterial vaginosis

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¹ The antibiotics and doses recommended in this chapter are based on those in *Therapeutic Guidelines: Antibiotic*, 13th edn, Therapeutic Guidelines Ltd, Melbourne, 2006.
with vulvovaginitis who presented to specialist pediatric services, only 10 had a probable infectious cause found.6

**Vulvovaginitis due to foreign body**
Foreign body characteristically results in foul-smelling discharge and requires an examination under anesthetic.4,5

**Vulvovaginitis due to Enterobius (pinworms or threadworms)**
Worm infestation with Enterobius (pinworms or threadworms) can cause a vulvovaginitis characterized by itch, including nighttime itch, redness, and scanty or no vaginal discharge.9 The diagnosis can be confirmed by placing sticky tape, to which the eggs adhere, on the anal mucosa. If confirmed or strongly suspected, we recommend:

- mebendazole 100 mg (child ≤ 10 kg: 50 mg) orally, as a single dose OR
- pyrantel 10 mg/kg (max 750 mg) orally, as a single dose

**Group A streptococcus vulvovaginitis**
Group A streptococcus can cause vulvovaginitis alone, or with perianal cellulitis, and/or with other manifestations of streptococcal infection, such as rash, fever, or sore throat.9,10 There is even one report of glomerulonephritis in association with group A streptococcal vulvovaginitis.11 The peak age of group A streptococcal vulvovaginitis is around 5 years.9,10 Erythema is usually prominent.9,10

If *S. pyogenes* is cultured, use:

- phenoxyethylpenicillin 10 mg/kg (max 500 mg) orally, 6-hourly

**Group B streptococcus (GBS) vulvovaginitis**
Colonization with GBS is common, usually asymptomatic, and does not correlate with sexual activity.12 A retrospective study of adolescent girls and young women who grew a pure growth of GBS found that 12 of 13 had purulent vaginal discharge and concluded that they had GBS vulvovaginitis.13 However, their swabs were taken because of symptoms, and the presence of GBS, which colonizes up to 30% of normal women, may have been coincidental and not causal. Most authorities would, however, treat an adolescent with purulent vaginal discharge who grew GBS with penicillin.

We recommend:

- phenoxyethylpenicillin 10 mg/kg (max 500 mg) orally, 6-hourly

**Neisseria gonorrhoeae vaginal infection**
Vaginal infection with *N. gonorrhoeae* is almost always symptomatic and results in a purulent green vaginal discharge, at least when it is a result of sexual abuse.14,15 Beyond the neonatal period, gonorrhea is always sexually acquired. In prepubertal girls it is acquired through child sexual abuse, and isolation of the organism is an absolute indication to make enquiries about child sexual abuse.16 The possibility of sexual abuse should be considered in any case for gonorrhea in a child of any age, from the neonatal period until adolescence.

The diagnosis of gonococcal infection can be suspected from gram stain and must be confirmed by culture of the organism.16 Although non-culture techniques such as polymerase chain reaction (PCR) are sensitive and specific,17 they are no better than culture, which is rapid and definitive. PCR for *N. gonorrhoeae* should be used on only urogenital specimens, and never on eye or throat specimens, when non-pathogenic Neisseriae can cause false-positive results. Where it is critical not to get false positives, as in likely medicolegal cases, culture is the only acceptable test.18 It is recommended to examine and take swabs from the oropharynx and anus as additional potential areas of infection.

Penicillin-resistance of *N. gonorrhoeae* is common, and eradication of unsuspected pharyngeal or anorectal infection is important.

**Question** | For the treatment of children with uncomplicated gonorrhea, is one antibiotic compared with others more effective?

**Literature review** | We found 23 RCTs of ceftriaxone, 9 RCTs and a review19 of ciprofloxacin, 7 RCTs of cefixime, 4 RCTs of ofloxacin, 3 RCTs of cefotaxime, and 3 RCTs of azithromycin.

A single dose of IM ceftriaxone has been studied most widely, and in 23 RCTs was 98–100% effective in treating uncomplicated gonorrhea and eradicating the organism, even when *N. gonorrhoeae* is penicillin-resistant. Ceftriaxone is the gold standard therapy to which other antibiotics are compared.
A single dose of IM cefotaxime was no different from IM ceftriaxone in three studies. Oral ciprofloxacin was found in a review to be effective, but a study from the Philippines reported 32% treatment failures when treating female sex workers with oral ciprofloxacin compared with 4% with oral cefixime, because of the emergence of ciprofloxacin resistance. Resistance to quinolones will also affect treatment with ofloxacin or gatifloxacain, but in the absence of quinolone resistance, ciprofloxacin, ofloxacin, and gatifloxacain have all been shown to be effective as ceftriaxone. Oral cefixime and oral azithromycin are both >95% effective in curing uncomplicated gonorrhea, including penicillin-resistant strains and in resource-poor settings.

We recommend:

- **ceftriaxone ≤ 45 kg:** 125 mg, >45 kg: 250 mg IM, as a single dose OR
- **cefotaxime 25 mg/kg (max 1 g)** IM, as a single dose OR
- **cefixime 20 mg/kg (max 800 mg)** orally, as a single dose OR
- **azithromycin 20 mg/kg (max 1 g)** orally, as a single dose

Because of increasing resistance, oral ciprofloxacin and other quinolones are no longer recommended, unless a sensitive strain has been identified.

The above treatment is ineffective against *Chlamydia*, with the exception of azithromycin (see below). We recommend excluding *Chlamydia* infection and, if it is not possible to exclude it, giving empiric treatment for *Chlamydia* infection (see below).

**Chlamydia trachomatis vulvovaginitis**

*C. trachomatis* infection is sexually acquired. Infection is often asymptomatic, but the detection of *C. trachomatis* in a child with vulvovaginitis is an indication for treatment and, if the child is prepubertal, for child sexual abuse enquiries and possible action.

*C. trachomatis* may be detected by non-culture techniques such as PCR or LCR (ligase chain reaction), which are highly sensitive, can be used on urine as well as genital secretions, and may thus be valuable in non-invasive screening for *Chlamydia*. LCR and PCR are more often positive than culture for *Chlamydia*, which means they are either more sensitive or detecting false positives (or both). However, none of the non-culture tests is approved or recommended by the manufacturers for rectogenital specimens from children. In addition to medical implications, the identification of *Chlamydia*, especially in a young child, also has legal implications. Because of the legal implications, the test needs to have the highest specificity, which is more important than sensitivity in this situation. Data on the specificity of these tests in prepubertal children are insufficient to permit their use at this time. Tests that are appropriate for screening a sexually active adult in a STD (sexually transmitted disease) clinic may not be appropriate for evaluating a child victim of suspected sexual abuse. Although missing possible sexual abuse is a major concern, the ramifications of a false-positive test for an STD, which can lead to erroneous accusations of sexual abuse, must also be considered.

If *Chlamydia* is identified by PCR or LCR on vaginal secretions of a girl with vulvovaginitis, we recommend treatment, but also recommend performing culture to confirm *Chlamydia* infection if the child is prepubertal or sexual abuse is suspected. Azithromycin is >95% effective, even in a resource-poor setting, and doxycycline is >90%. We recommend:

- **azithromycin 20 mg/kg (max 1 g)** orally, as a single dose OR
- **doxycycline (>8 years):** 2.5 mg/kg (max 100 mg) orally, 12-hourly for 7 days

Sexual partners should be traced and treated, if possible.

**Vulvovaginal candidiasis**

Vulvovaginal candidiasis is rare in prepubertal girls with vulvovaginitis, but becomes increasingly common thereafter. Up to 75% of women of child-bearing age develop acute vulvovaginal candidiasis, which becomes chronic in 5–10%. Effective topical preparations include nystatin and azoles (clotrimazole, econazole, miconazole), which are comparable in efficacy. Topical clotrimazole is 95% effective in treating acute candidal vulvovaginitis. Oral itraconazole is as effective as topical clotrimazole, but fluconazole is somewhat less effective. In an RCT which looked at recurrence rates after 6 months, the most successful treatment with a cure rate of 81% was miconazole vaginal cream with oral nystatin. Occasionally, topical therapy may itself cause irritation. Nystatin, although marginally
less effective, is generally better tolerated than the imidazoles.\textsuperscript{33} We recommend:

- **topical clotrimazole vaginal cream or pessary** OR
- **topical nystatin vaginal cream or pessary**

The use of preparations that also contain topical steroids can relieve irritation.

If the patient is intolerant of topical therapy or would prefer to use oral therapy, or infection recurs and the patient is not pregnant, 1-day treatment with either fluconazole\textsuperscript{34} or itraconazole\textsuperscript{36} is effective. We recommend:

- **fluconazole 4 mg/kg (max 150 mg) orally, as a single dose** OR
- **itraconazole 5 mg/kg (max 200 mg) orally**

  12-hourly for 1 day (best taken with an acid drink such as Coca Cola to improve absorption)

If the initial treatment fails, we recommend reviewing the diagnosis and seeking specialist advice.

Symptomatic sexual partners (usually balanitis in the uncircumcised male) should be treated with a topical antifungal plus a topical corticosteroid (see Section 13.1, p. 211).

**Trichomonas vulvovaginitis**

Trichomoniasis is an STD of post-menarchal girls and women.\textsuperscript{37} Symptomatic women complain of vaginal discharge, pruritus, and irritation. Signs of infection include pale yellow to gray-green vaginal discharge (42%), fishy or musty odor (50%), and edema or erythema (22–37%).\textsuperscript{37} The discharge is classically described as frothy, but it is actually frothy in only about 10% of patients.\textsuperscript{37} Colpitis macularis (strawberry cervix) is a specific clinical sign for this infection, but is detected with reliability only by colposcopy and rarely during routine examination. Other complaints may include dysuria and lower abdominal pain. Most adolescents and women with trichomoniasis also have bacterial vaginosis.\textsuperscript{37,38} Nearly half of all women with *Trichomonas vaginalis* are asymptomatic.\textsuperscript{37}

Male partners are usually asymptomatic, but can develop urethritis, and rarely epididymitis or prostatitis.\textsuperscript{37} Empiric treatment of partners is indicated. Investigation for other sexually transmitted infections should be considered. Metronidazole and tinidazole are both effective in >95% of cases.\textsuperscript{37} We recommend:

- **metronidazole 50 mg/kg (max 2 g) orally, as a single dose** OR
- **tinidazole 50 mg/kg (max 2 g) orally, as a single dose**

In one study, 20 patients with clinically refractory trichomoniasis (failure to respond to therapy with oral metronidazole using at least 500 mg twice a day for 7 days) were treated with high doses of oral and vaginal tinidazole (2–3 g orally plus 1–1.5 g intravaginally for 14 days). The cure rate was 92% and no patients discontinued therapy due to side effects.\textsuperscript{39}

**Bacterial vaginosis**

Bacterial vaginosis is a condition of sexually active adolescents and women, characterized by changes in vaginal flora. The clinical diagnosis requires three of the following: a white, non-inflammatory, vaginal discharge; vaginal pH >4.5; a fishy odor before or after adding 10% hydrogen peroxide (the “whiff test”); presence of “clue cells” on microscopy of vaginal secretions (squamous epithelial cells covered with bacteria resulting in ragged edges).\textsuperscript{40–42} Bacterial vaginosis in pregnancy is associated with preterm birth,\textsuperscript{41} but meta-analyses of trials of treating bacterial vaginosis with antibiotics have consistently failed to show a reduction in preterm births.\textsuperscript{42}

Metronidazole vaginal gel is as effective as oral metronidazole and is associated with fewer gastrointestinal complaints.\textsuperscript{43} We recommend:

- **metronidazole 0.75% gel intravaginally, once daily for 5 days**

**13.3 Epididymo-orchitis**

Acute epididymo-orchitis can cause swelling, redness, and pain in the testis and/or epididymis. It is rare in young children\textsuperscript{44,45} and needs to be distinguished clinically from testicular torsion.\textsuperscript{46} Boys with epididymo-orchitis are more likely to have a tender epididymis and some scrotal swelling and redness without pain, whereas boys with torsion are more likely to have a tender testicle and an absent cremasteric reflex.\textsuperscript{46} High-resolution ultrasound with an experienced investigator
is able to exclude torsion reliably\textsuperscript{45} so that routine surgical exploration is seldom necessary.

Testicular swelling can also occur with edema due to nephrotic syndrome, due to malignancy, and as a manifestation of Henoch–Schonlein purpura.

Epididymo-orchitis can occur in infancy and in boys aged 10–15 years.\textsuperscript{44,45} It is rare to find a cause, although there may be underlying urinary tract problems and urine cultures occasionally grow a pathogen, such as \textit{Escherichia coli}. Urinalysis and urine culture should be performed on all children with acute epididymo-orchitis.\textsuperscript{45}

In adolescents and young men, acute epididymo-orchitis is usually either a complication of genitourinary infection with enteric Gram-negative bacteria or a complication of a sexually transmitted urethral infection, such as \textit{C. trachomatis}\textsuperscript{47,48} or \textit{N. gonorrhoeae}.\textsuperscript{47} Rarely, it occurs by hematogenous spread as a complication of a systemic infection. Genitourinary tuberculosis may present as epididymo-orchitis, with scrotal pain, swelling, and often sinuses.\textsuperscript{49}

For mild to moderate infection from a probable urinary tract source, we recommend:

\textit{cephalexin 12.5 mg/kg (max 500 mg) orally, 12-hourly for 14 days OR trimethoprim 4 mg/kg (max 150 mg) orally, 12-hourly for 14 days}

If resistance to the above drugs is suspected or proven, we recommend:

\textit{norfloxacin 10 mg/kg (max 400 mg) orally, 12-hourly for 14 days}

If infection is thought to be sexually acquired, \textit{C. trachomatis} (D–K serovars) or \textit{N. gonorrhoeae} are usually involved, although in men who are the insertive partner during anal intercourse, epididymitis can be caused by sexually transmitted enteric organisms (e.g., \textit{E. coli}). We recommend taking appropriate specimens (urethral exudate or swab or first-void urine) before starting empiric therapy with:

\textit{ceftriaxone \leq 45 kg: 125 mg, >45 kg: 250 mg IM, as a single dose OR cefotaxime 25 mg/kg (max 1 g) IM, as a single dose OR cefixime 20 mg/kg (max 800 mg) orally, as a single dose OR azithromycin 20 mg/kg (max 1 g) orally, as a single dose}

If adherence to 2 weeks of doxycycline or roxithromycin is unlikely, there are theoretical grounds for using azithromycin 25 mg/kg (max 1 g) orally on days 1 and 8, although no clinical trial has assessed this.

### 13.4 \textit{Neisseria gonorrhoeae} infections

Infection with \textit{N. gonorrhoeae}\textsuperscript{49} can occur at the following ages:

- **Neonatal:** Usually ophthalmic, but can cause vaginitis, scalp abscess, or disseminated bacteremic disease involving joints and meninges
- **Prepubertal** (usually due to child sexual abuse): Vaginitis, less commonly pelvic inflammatory disease (PID), hepatitis, rarely anorectal, and tonsillopharyngeal
- **Sexually active adolescents:** Girls may be asymptomatic or develop urethritis, endocervicitis, and salpingitis, and boys usually develop symptomatic urethritis. Rectal and pharyngeal infections are often asymptomatic.

For diagnosis and rationale for treatment, see p. 212. For uncomplicated infection, we recommend:

\textit{cefinome 25 mg/kg (max 1 g) IM, as a single dose OR cefotaxime 25 mg/kg (max 1 g) IM, as a single dose OR cefixime 20 mg/kg (max 800 mg) orally, as a single dose OR azithromycin 20 mg/kg (max 1 g) orally, as a single dose}

### 13.5 Syphilis

Congenital syphilis can cause still birth, preterm birth, hydrops fetalis, and intrauterine growth retardation. Other manifestations at birth or developing in early infancy include bullous rash, anemia, hepatosplenomegaly, edema, snuffles, and osteitis presenting as pseudoparalysis of a limb or limbs. Late manifestations of untreated congenital syphilis include Hutchinson triad of Hutchinson teeth (notched central incisor), sensorineural deafness, and interstitial keratitis, and also saddle nose, rhagades (fissured skin around the mouth), anterior shin bowing, and Clutton joints (symmetric painless swelling of the knees).\textsuperscript{31,52}
Acquired primary syphilis results in chancres, which are painless indurated ulcers of the mucous membranes or skin at the site of infection, usually the genitalia.53

Secondary syphilis, which develops 1–2 months later, causes a generalized maculopapular rash usually involving palms and soles, papular lesions called condyloma lata in moist areas around the vulva or anus, and regional or generalized lymphadenopathy. The patient may have systemic manifestations such as fever, malaise, arthralgia, sore throat, and splenomegaly.53

Disease then becomes latent, with serologic evidence of infection but no clinical manifestations, although the symptoms of secondary syphilis may recur. Late syphilis can be tertiary, with gumma formation and aortitis from cardiovascular syphilis, or can cause neurosyphilis, which is particularly likely in association with human immunodeficiency virus (HIV) infection.53

The diagnosis of syphilis is usually made serologically,53,54 although dark ground microscopy and PCR on clinical specimens are also valuable.55

Specific serologic tests for Treponema pallidum are the fluorescent treponemal antibody absorption and the T. pallidum particle agglutination tests. These antibody tests remain reactive for life, even after successful treatment, so should not be used to indicate response to treatment.53,54 False positives can occur with other treponemal disease including yaws and rat-bite fever and with Lyme disease.53,54

Non-specific (non-treponemal) tests are the Vener- real Disease Research Laboratory (VDRL), the rapid plasma reagin test (RPR), and the automated reagin test (ART). They are cheap and rapid and give quantitative results, which are useful to monitor response to treatment. They are usually used for screening for syphilis, and specific tests are done if the non-specific test is positive. False negatives can occur in early primary disease, latent disease, and late congenital syphilis, while false positives can occur in a number of other conditions including EBV infection, SLE, and lymphoma.53,54

If in doubt about serology results, which can be very confusing, we recommend asking advice from a microbiologist. The need for long-term follow-up with repeat serology and the frequent presence of complicating factors makes it desirable to seek specialist advice, particularly for patients who are pregnant, have HIV infection, or are allergic to penicillin.

### Treatment of syphilis
Penicillin remains the drug of choice for syphilis, and there are few alternatives. A single dose of oral azithromycin was as effective as benzathine penicillin in early syphilis in three trials.56–58 A small study found that ceftriaxone and penicillin G were equally effective for primary and secondary syphilis,59 while a pilot study found ceftriaxone to be as effective as penicillin G for HIV-infected patients with neurosyphilis, but differences in the two groups limited comparisons between them.60 Penicillin desensitization should be performed whenever practicable for patients who are allergic to penicillin. If drugs other than penicillin are used, careful follow-up is recommended.

### Pregnancy and congenital syphilis
Pregnant patients should be treated with penicillin in the dosage schedule recommended for non-pregnant patients at a similar stage of the disease.51,52,61 We recommend desensitizing patients who are allergic to penicillin or seeking specialist advice. Tetracyclines should never be used in pregnancy or in the newborn, and erythromycin does not reliably treat an infected fetus.

If a mother with positive serology or active syphilis receives adequate penicillin treatment before 28 weeks’ gestation (and her partner is adequately treated simultaneously) and she is not reinfected, the risk of congenital syphilis is low, but the baby should still be examined and investigated at birth, and the placenta examined by direct immunofluorescence and silver stains.51,52

Cord blood is inadequate for screening.51,52 All infants of seropositive mothers should be examined carefully, and a quantitative non-treponemal syphilis antibody test (VDRL or RPR) should be done on baby’s and mother’s blood.51,52

Because of the risk from untreated congenital syphilis,51,52,61 the baby should be treated empirically unless all the following apply:
- Mother was adequately treated (with an appropriate penicillin regimen, not with a non-penicillin such as erythromycin).
- Mother was treated >1 month before delivery (treatment failures can occur).
- Mother’s antibody titers fell after treatment and remain low at delivery (reinfection can occur).
- The baby’s physical examination is normal.
The baby’s VDRL or RPR is low and no higher than the mother’s.

Follow-up is assured.

If the mother’s titer has risen fourfold, or the baby’s titer is fourfold higher than the mother’s, or the baby’s examination is abnormal, it is recommended to perform liver function tests, long bone radiographs, and a CSF (cerebrospinal fluid) microscopy and VDRL on the baby.51,52,61

All newborns of mothers with syphilis should be investigated and treated in consultation with a specialist. For the treatment of congenital syphilis, we recommend:

**benzylpenicillin (aqueous crystalline penicillin G) 30 mg/kg or 50,000 U/kg IV, 12-hourly for 7 days, then 8-hourly for 3 days OR**

**procaine penicillin 30 mg/kg or 50,000 U/kg IM, daily for 10 days**

There have been two small studies that suggest that a single dose of benzathine penicillin (50,000 U/kg IM) may be adequate to treat asymptomatic babies at risk of syphilis.62,63 A South African study of asymptomatic babies whose mothers had VDRL titers of 32 or more found that 4 of 8 untreated babies developed congenital syphilis, but none of 11 given benzathine penicillin.62 A North American study found that a single dose of benzathine penicillin and 10 days of procaine penicillin were equally effective, although neither was 100% effective.63 IV benzylpenicillin for 10 days is kinder than 10 days of IM procaine penicillin, is known to be effective, including treating and preventing neurosyphilis (procaine penicillin may not give adequate CSF levels64), and is the recommended treatment of choice for congenital syphilis.51,52,61

**Early syphilis**

Early syphilis is defined as primary (chancre), secondary (rash or condylomata lata), or latent (asymptomatic syphilis confirmed to be <2 years duration, based on serology results). We recommend:

**benzathine penicillin 30 mg/kg or 50,000 U/kg (max 1.5 g or 2.4 million U) IM, as a single dose OR**

**procaine penicillin 30 mg/kg or 50,000 U/kg (max 1.5 g or 2.4 million U) IM, daily for 10 days**

For nonpregnant patients who are allergic to penicillin and in whom desensi-tization is not possible, azithromycin has been shown to be effective in RCTs in industrialized56 and developing countries.57,58 Ceftriaxone appears to be as effective, but data are more limited.59,60 There are no RCTs of tetracyclines in syphilis. We recommend:

**azithromycin 50 mg/kg (max 2 g) orally, as a single dose**

Careful clinical and serologic follow-up is essential.

Pregnant patients who are allergic to penicillin should be desensitized and treated with penicillin.

We recommend advising the patient to avoid sexual activity until lesions are healed. Sexual contacts within the last 3 months should have the same treatment even if their serology is negative.

HIV-infected patients with early syphilis are at increased risk for neurological complications.64–66 They should be evaluated clinically and serologically at 6-monthly intervals for at least 2 years after therapy. If, at any time, clinical symptoms develop or non-treponemal titers rise fourfold, a repeat CSF examination should be performed and treatment administered accordingly.66 Some specialists recommend additional treatments in HIV-positive patients (e.g., benzathine penicillin administered at 1-week intervals for 3 weeks, as recommended for late syphilis).66

**Late latent syphilis**

Late latent syphilis is defined as latent syphilis of >2 years or indeterminate duration, in the absence of tertiary syphilis. Specialist advice should be sought regarding the need for and interpretation of lumbar puncture. This is particularly important for situations with treatment failure or HIV infection. For treatment, use:

**benzathine penicillin 30 mg/kg or 50,000 U/kg (max 1.5 g or 2.4 million U) IM, once weekly for three doses**

We recommend a CSF examination before treatment for HIV-infected patients with late latent syphilis or syphilis of unknown duration, because of the increased risk of neurosyphilis with HIV infection.66 If the CSF examination is normal, treat with benzathine penicillin as above, but if abnormal we recommend to treat and manage as for neurosyphilis66 (see p. 218).
Tertiary syphilis and neurosyphilis
Tertiary syphilis includes cardiovascular syphilis and gummatas. Neurosyphilis is diagnosed on CSF findings. Specialist advice should be sought. Use:

benzylpenicillin 60 mg/kg or 100,000 U/kg (max 2.4 g or 4 million U) IV, 4-hourly for 14 days OR
procaine penicillin 60 mg/kg or 100,000 U/kg (max 2.4 g or 4 million U) IM, daily for 14 days

When treating cardiovascular or neurosyphilis, prednisolone 0.5 mg/kg (max 20 mg) orally, 12-hourly for three doses may be administered with penicillin to reduce the likelihood of a Jarisch–Herxheimer reaction.53

13.6 Genital herpes simplex virus (HSV) infection

Genital herpes is sexually acquired and characterized by vesicular or ulcerative lesions of the genitalia and sometimes the perineum, although infection may be asymptomatic.67 It can be caused by HSV-1 or 2. The diagnosis is made by viral culture from swabs of the genitalia or by rapid diagnostic tests, such as immunofluorescence or PCR.68,69 Patients should have a full screen for sexually transmissible infections (including HIV serology) on their first presentation.

Oral acyclovir reduces systemic symptoms and shortens viral shedding in first episode genital herpes, but does not reduce the incidence of subsequent recurrences.70 We could find no studies comparing valacyclovir or famciclovir with acyclovir for acute genital HSV infection. However, the evidence from studies of recurrent genital herpes suggests that the three drugs are therapeutically equivalent. Ease of administration, availability, and cost should be considered when choosing therapy.

Initial acute episode of genital herpes
For a first clinical episode, after taking a swab for culture, immunofluorescence, or PCR, we recommend:

acyclovir 10 mg/kg (max 400 mg) orally, 6-hourly for 7 days (preferred in pregnancy) OR (only if >12 years)

famciclovir 250 mg orally, 8-hourly for 7 days OR (only if >12 years)

valacyclovir 1 g orally, 12-hourly for 7 days

Recurrent genital herpes
Infrequent but severe recurrences can be treated with episodic therapy, commenced at the onset of prodromal symptoms or within a day. Acyclovir is as effective as famciclovir71 and valacyclovir.72 Studies on duration of therapy have shown effective treatment with 2 days of acyclovir,73 3 days of valacyclovir,74 and a single day of patient-initiated famciclovir.75 We recommend:

acyclovir 20 mg/kg (max 800 mg) orally, 8-hourly for 2 days (preferred in pregnancy) OR (only if >12 years)

famciclovir 1 g orally, 12-hourly for 1 day OR (only if >12 years)

valacyclovir 500 mg orally, 12-hourly for 3 days

Suppressive treatment may be indicated for frequent, severe recurrences. Suppression reduces recurrences by 70–80%.76 Transmission of HSV can still occur. We recommend:

acyclovir 5 mg/kg (max 200 mg) orally, 12-hourly OR (only if >12 years)

famciclovir 250 mg orally, 12-hourly (500 mg orally, 12-hourly in immunocompromised patients) OR (only if >12 years)

valacyclovir 500 mg orally, daily (1 g orally, daily in immunocompromised patients)

If frequent breakthrough infections occur during prophylaxis, higher doses may be successful. Treatment may be interrupted every 6 months to determine the natural history of the disease in any given patient, and can be restarted in the event of frequent recurrences.

13.7 Human papillomavirus (HPV) infection

HPV infection in the genital tract is largely asymptomatic and transient.77 It can be detected only by cellular changes seen by cytology of the Papanicolaou (Pap) smear or at colposcopy, or by HPV DNA testing.77 There are 30–40 HPV genotypes that infect the genital area. These are divided into high-risk (or oncogenic) and low-risk genotypes.77

HPV's cause cervical cancer. Persistent infection with one of the oncogenic genotypes is a prerequisite for the development of high-grade cervical intraepithelial neoplasia (CIN2 or CIN3), which is the precursor to cervical cancer.77 Genotypes 16 and 18 are the
most important genotypes, responsible for 70% of cervical cancers, and have been incorporated into HPV vaccines.\textsuperscript{78,79} Low-grade cervical dysplasia (CIN1) is benign.\textsuperscript{77}

Infection of males with oncogenic HPV can rarely result in cancer of the penis.\textsuperscript{77}

Low-risk HPV genotypes 6 and 11 cause more than 90% of genital warts (condylomata acuminata) in both sexes, but do not cause cervical cancer.\textsuperscript{77} However, the presence of genital warts indicates sexual activity and a risk of exposure to oncogenic HPV. It is important for all female patients with genital warts to have regular Pap smears.\textsuperscript{77} The presence of anogenital warts may be an indicator of child sexual abuse, and affected children should be examined and tested for other sexually transmitted infections.\textsuperscript{77}

Vaccines have been developed using virus-like particles. One vaccine\textsuperscript{79} contains HPV 16 and 18, while another vaccine\textsuperscript{78} contains HPV 6, 11, 16, and 18. Both vaccines have been shown in RCTs to be highly effective.\textsuperscript{78,79} These vaccines will be introduced routinely for schoolgirls and possibly schoolboys and uninfected sexually active young women in industrialized countries.\textsuperscript{77}

### 13.8 Pelvic inflammatory disease

The term “pelvic inflammatory disease” denotes a spectrum of inflammatory disorders of the female genital tract, including endometritis, chorioamnionitis, intraamniotic syndrome, salpingitis, oophoritis, tubo-ovarian abscess, and pelvic peritonitis.\textsuperscript{80,81} Infections can vary from mild to life-threatening. Empiric treatment for PID is recommended in sexually active young women with uterine or adnexal tenderness or cervical motion tenderness if no other cause can be identified.\textsuperscript{81}

Pelvic infection in females is usually sexually acquired or results from complications associated with pregnancy. Infection is usually polymicrobial. A meta-analysis of 34 studies of variable quality published between 1966 and 1992 showed that a number of treatment regimens were effective.\textsuperscript{82} A subsequent RCT showed that 14 days of azithromycin was at least as effective as regimens using metronidazole+doxycycline+cefoxitin+probenecid or doxycycline+amoxicillin/clavulanate for up to 21 days.\textsuperscript{85} A number of different regimens are recommended by the CDC (Centers for Disease Control and Prevention) for both ambulatory and parenteral treatment, while acknowledging that the evidence for them is scanty.\textsuperscript{84}

For severe infections, we recommend:

- azithromycin 12.5 mg/kg (max 500 mg) IV, daily for 1–2 days, then azithromycin 10 mg/kg (max 400 mg) orally, daily for 14 days OR
cefotetan 40 mg/kg (max 2 g) IV, 12-hourly OR
THE COMBINATION OF
amoxicillin/ampicillin 50 mg/kg (max 2 g) IV, 6 hourly
PLUS
gentamicin 6 mg/kg IV, daily PLUS
metronidazole 12.5 mg/kg (max 500 mg) IV, 12-hourly

For mild to moderate infection, we recommend:

- azithromycin 10 mg/kg (max 400 mg) orally, daily for 14 days OR
amoxicillin+clavulanate 22.5 + 3.2 mg/kg (max 875 + 125 mg) orally, 12-hourly for 14 days PLUS
doxycycline 2.5 mg/kg (max 100 mg) orally, 12-hourly for 14 days

### 13.9 Post-sexual assault prophylaxis

Following sexual assault, the victim should be assessed and examined by an expert. Evidence-based guidelines have been published.\textsuperscript{85} The examiner may decide to conduct tests for STDs, although this is not inevitable. Approximately 5% of sexually abused children acquire an STD as a result of the abuse.\textsuperscript{85,86}

Universal screening of post-pubertal patients for STDs is recommended,\textsuperscript{87} but more selective criteria may be appropriate for testing prepubertal patients.\textsuperscript{85} For example, the yield of positive gonococcal cultures is low in asymptomatic prepubertal children, especially when the history indicates only fondling.\textsuperscript{88} Vaginal samples are adequate for STD testing in prepubertal children, whereas cervical samples are recommended in post-pubertal children.\textsuperscript{85,86}

It is recommended to test before initiating any prophylactic treatment, for legal as well as treatment reasons.\textsuperscript{85,86} The most specific and sensitive tests should be used when evaluating children for STDs. Cultures are considered the “gold standard” for diagnosing C. trachomatis (cell culture) and N. gonorrhoeae (bacterial culture). New tests such as nucleic
Post-sexual assault antibiotic prophylaxis

Antibiotic prophylaxis is not generally recommended, unless the person committing the assault is known to be suffering from or at high risk of a sexually transmitted infection. If it is decided to give prophylaxis, we recommend:

- **ceftriaxone**: ≤45 kg: 125 mg, >45 kg: 250 mg IM, as a single dose PLUS
- **azithromycin**: 20 mg/kg (max 1 g) orally, as a single dose PLUS EITHER
- **metronidazole**: 50 mg/kg (max 2 g) orally, as a single dose OR
- **tinidazole**: 50 mg/kg (max 2 g) orally, as a single dose

Post-sexual assault HIV prophylaxis

An estimate of the pooled risk of acquiring HIV after a single act with an HIV-infected person, based on observational studies, is given in Table 13.1. Knowledge of the risk helps when deciding or counseling about prophylaxis. Although efficacy of post-exposure prophylaxis against HIV infection is unknown for sexual abuse, prophylaxis is effective in needlestick injuries (see Section 8.9, p. 112) and is recommended for unprotected receptive or insertive anal or vaginal intercourse if the person committing the assault is known or suspected to be infected with HIV. Initiation of prophylaxis should be the responsibility of, or be undertaken after taking advice from, an experienced HIV physician.

If it is decided to give HIV prophylaxis, we recommend:

- lamivudine 4 mg/kg (max 150 mg) AND
- zidovudine 8 mg/kg (max 300 mg) orally,
  12-hourly for 4 weeks or until source shown to be HIV negative PLUS EITHER
- lopinavir 300 mg/m² (max 400 mg) AND
- ritonavir 75 mg/m² (max 100 mg), orally,
  12-hourly (Kaletra) for 4 weeks or until source shown to be HIV negative OR
- nelfinavir <13 years 55 mg/kg (max 2 g) orally,
  12-hourly; >12 years 1250 mg orally, 12-hourly for 4 weeks or until source shown to be HIV negative

<table>
<thead>
<tr>
<th>Route of Exposure</th>
<th>Risk per 1000 Exposures</th>
</tr>
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<tbody>
<tr>
<td>Receptive anal intercourse</td>
<td>5</td>
</tr>
<tr>
<td>Receptive penile vaginal intercourse</td>
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</tr>
<tr>
<td>Insertive anal intercourse</td>
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</tr>
<tr>
<td>Insertive penile vaginal intercourse</td>
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</tr>
<tr>
<td>Receptive oral intercourse</td>
<td>0.1</td>
</tr>
<tr>
<td>Insertive oral intercourse</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Adapted from References 89–91.

Post-sexual assault hepatitis B virus (HBV) prophylaxis

If the child is not fully immunized against HBV, or their vaccine status is unknown, we recommend hepatitis B immunoglobulin and a course of hepatitis B vaccine.

References

50 Woods CR. Gonococcal infections in neonates and young children. Semin Pediatr Infect Dis 2005;16:258–70.
Sexually transmitted and genital infections

CHAPTER 14
Skin and soft tissue infections

Evidence-based practice guidelines on the management of skin and soft tissue infections have been developed by the Infectious Disease Society of America.¹

14.1 Bites: dog, cat, and human bites

Bites often become infected. The rate of infection is highest for cat and human bites. In a Cochrane review of prophylactic antibiotics, the rates of infection without antibiotics were 67% for cat bites and 47% for human bites.² The rate for dog bites was 5.5% in the Cochrane review,² but 16% in a meta-analysis of prophylactic antibiotics for dog bites.³

A study of human and animal bites in children found that most wounds were polymicrobial and were infected with both aerobic and anaerobic organisms.⁴ The most frequent isolates in both types of bite wounds were *Staphylococcus aureus*, anaerobic cocci, and bacteroides spp. *Pasteurella multocida* and *Pseudomonas fluorescens* were present only in animal bites, while group A streptococci were present only in human bites. Beta-lactamase-producing organisms were common. This study demonstrates the polymicrobial aerobic–anaerobic nature of human and animal bite wounds.

In a study of infected cat and dog bites, *Pasteurella* species were the most frequent isolates from both dog bites (50%) and cat bites (75%): *P. canis* was the most common isolate from dog bites, and *P. multocida* from cat bites.⁵ Other common aerobes included streptococci, staphylococci, Moraxella, and Neisseria. Common anaerobes included fusobacterium, bacteroides, porphyromonas, and prevotella.

Thorough wound cleaning and debridement of devitalized tissue is advised, with operative wound exploration if necessary.⁶ This advice follows basic microbiologic principles, although we could not find any controlled trials.

Prophylactic antibiotics for dog, cat, and human bites

**Question**  | For children with dog, cat, or human bites, do prophylactic antibiotics compared with no prophylactic antibiotics or placebo reduce the risk of infection?

**Literature review**  | We found eight RCTs and one Cochrane review² of prophylactic antibiotics for mammalian bites. We found a non-Cochrane meta-analysis of trials of prophylactic antibiotics for dog bites.³ We found one RCT of prophylactic antibiotics for cat bites⁷ and one RCT for human bites to the hand.⁸

The Cochrane review of prophylactic antibiotics for bites from mammals (animals and humans) found eight RCTs, which met the search criteria, six of them included dog bites.² For dog bites, there was no statistically significant reduction of infection rate after the use of prophylactic antibiotics (10/225 or 4%) compared to the control group (13/238 or 5.5%; OR 0.74, 95% CI 0.30–1.85). However, a separate meta-analysis of dog bites, including two additional studies, which did not meet Cochrane criteria, reached a different conclusion.³ The estimated cumulative incidence of infection in controls in the eight studies was 16%. The relative risk for infection in patients given antibiotics compared with controls was 0.56 (95% CI 0.38–0.82), and about 14 patients must be treated to prevent one infection.³ The evidence for prophylactic antibiotics for dog bites is fairly weak.

The Cochrane review identified one small RCT of oxacillin for cat bites.⁷ The infection rate in the control group was 67% (4/6) compared with none of five in the prophylactic antibiotic group (p = 0.045). Material

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¹ The antibiotics and doses recommended in this chapter are based on those in *Therapeutic Guidelines: Antibiotic*, 13th edn, Therapeutic Guidelines Ltd, Melbourne, 2006.
obtained from three of the four infected patients grew *P. multocida*.7

The Cochrane review identified only one human study, of bites to the hand, in which patients received oral or parenteral antibiotics or no antibiotics.8 The infection rate in the antibiotic group (0/33) was significantly lower than the infection rate in the control group (7/15 or 47%; OR 0.02, 95% CI 0–0.33).

Time since the bite is also important. An RCT compared amoxicillin-clavulanate with placebo in full-thickness animal bite wounds in a series of 185 consecutive patients.9 In wounds less than 9 hours old, no significant benefit was found with antibiotic. The infection rate was reduced significantly in wounds presenting 9–24 hours after injury, although the numbers were small.

Antibiotics may not be necessary for mild dog bites not involving tendons or joints that can be adequately debrided and irrigated within 8 hours.

We recommend prophylactic antibiotics in the following circumstances:

- cat bites;
- human bites;
- bites from dogs and other mammals with delayed presentation (≥ 8 hours);
- bite wounds that cannot be debrided adequately;
- bites on hands, feet, or face;
- bites involving underlying structures, such as bones, joints, or tendons;
- bites in immunocompromised patients.

If the wound is obviously infected, a wound swab should be taken, and consideration should be given to delaying primary wound closure.6

For oral antibiotics, we recommend:

**amoxicillin + clavulanate 22.5 + 3.2 mg/kg (max 875 + 125 mg) orally, 12-hourly for 5 days**

If there is likely to be delay in starting oral antibiotics and there is a need to start treatment urgently, we recommend:

**procaine penicillin 50 mg (80,000 U)/kg (max 1.5 g or 2.4 million U) IM, as a single dose, followed by oral amoxicillin + clavulanate, as above**

or alternatively:

**clindamycin 10 mg/kg orally or IV, 8-hourly**

For severe and penetrating injuries, it is advised to commence with parenteral treatment1,6,10 to change to oral antibiotics (amoxicillin-clavulanate unless cultures dictate differently) when improving, and continue antibiotics (IV+oral) for a total of 14 days.10 We recommend:

**metronidazole 10 mg/kg (max 400 mg) orally, 12-hourly PLUS EITHER**

**ceftriaxone 25 mg/kg (max 1 g) IV, daily OR**

**cefotaxime 25 mg/kg (max 1 g) IV, 8-hourly**

Alternatively, as a single preparation, use:

**piperacillin + tazobactam 100 + 12.5 mg/kg (max 4 + 0.5 g) IV, 8-hourly OR**

**ticarcillin + clavulanate 50 + 1.7 mg/kg (max 3 + 0.1 g) IV, 6-hourly OR**

**ampicillin + sulbactam 50 mg/kg (max 2 g) IV, 6-hourly**6 (not licensed for children)

For patients with anaphylactic penicillin allergy, we recommend:

**metronidazole 10 mg/kg (max 400 mg) IV or orally, 12-hourly PLUS**

**ciprofloxacin 10 mg/kg (max 500 mg) IV or orally, 12-hourly**

The recommendations regarding prophylactic antibiotics for bites from other mammals such as rats and raccoons are less clear-cut, because they have not been studied so systematically. However, because the risk of spirochetal infection following rat bite is about 10%, some authorities recommend penicillin prophylaxis.11 The need for immunization should always be considered (see below).

Human immunodeficiency virus (HIV) prophylaxis should be considered for children exposed to HIV by a bite (see p. 112).

**Immunization of the child with a mammalian bite**

The major considerations for prevention by immunization are rabies, tetanus, and hepatitis B.

Bats and raccoons are known to carry rabies (or Lyssavirus in Australia), and if a child is bitten by an animal that might be rabid, we recommend strong consideration of post-exposure prophylaxis against rabies.1,6,11–13
For children who have received their primary immunizations including tetanus, a dose of tetanus toxoid (or dT or DTP) is advised only if the child has not had a fourth dose. For children who have had fewer than three doses of tetanus, a dose of tetanus toxoid is recommended. Tetanus toxoid is recommended for unimmunized children and if immunization status is unknown. Tetanus immunoglobulin should be considered for unimmunized or partially immunized children, depending on the severity of the bite.1,6,11–13

The risk of hepatitis B should be assessed. We recommend giving vaccine and immunoglobulin to unimmunized children exposed to hepatitis B virus (see p. 93).

### 14.2 Bites: reptile bites

Reptile bites from sharks,14 alligators,15 and large reptiles16 are associated with water-loving, Gram-negative bacilli, including Vibrios, Aeromonas, Klebsiella, *Escherichia coli*, and anaerobes. All reptile bites, including snake bites, should prompt the clinician to consider the child’s tetanus status. Antibiotic prophylaxis is advised for most reptile bites, because of the high rate of wound infection.6,15

For oral prophylaxis, we recommend:

- **Ciprofloxacin 10 mg/kg (max 500 mg) orally, 12-hourly**

For severe bites requiring hospitalization, we recommend:

- **Ciprofloxacin 10 mg/kg (max 400 mg) IV, 12-hourly OR Cefotaxime 50 mg/kg (max 2 g) IV, 8-hourly**

### 14.3 Anthrax

*Bacillus anthracis* is an aerobic Gram-positive, spore-forming bacillus. It produces exotoxins, which cause hemorrhage, edema, and necrosis. Natural infection occurs as a zoonosis, from contact with infected animals or contaminated animal products, such as hides, wool, or meat. Anthrax can also be spread by bioterrorism. Anthrax can be cutaneous, inhalational, or gastrointestinal.17–19

In cutaneous anthrax, a pruritic papule or vesicle at the entry site develops 1–12 days after contact, and enlarges and ulcerates in 1–2 days, forming a painless ulcer with a black scab (eschar). There is a variable degree of surrounding edema, hyperemia, and regional lymphadenopathy. The eschar generally separates and sloughs after 12–14 days. Swelling surrounding the lesion can be minor or severe (i.e., malignant edema). Mild-to-moderate fever, headaches, and malaise often accompany the illness. Cultures of untreated lesions, depending on the stage of evolution, have positive results >80% of the time.17–19

There are no RCTs of therapy of cutaneous anthrax. Most published data indicate that penicillin is effective therapy and will “sterilize” most lesions after a few hours to 3 days, but does not accelerate healing.17–19 Its value seems to be primarily reducing mortality from as high as 20% to 0%. In vitro and animal studies suggest that ciprofloxacin and doxycycline should be effective.17–19

For naturally occurring anthrax, penicillin is effective in >90% of children.20 We recommend:

- **Phenoxymethylpenicillin (penicillin V) 10 mg/kg (max 500 mg) orally, 6-hourly for 7–10 days**

For bioterrorism-associated cutaneous disease, it is recommended to use ciprofloxacin 10–15 mg/kg (max 500 mg) orally, 12-hourly, or doxycycline 2.5 mg/kg (max 100 mg) orally, 12-hourly until susceptibility data are known.17–19 The rationale is that genetically altered *B. anthracis* might be resistant to penicillin. So far, there is no evidence of penicillin-resistant bioterrorist strains, and there are animal studies but no clinical evidence in humans to support the use of ciprofloxacin and doxycycline.17–19

Initiation of intravenous therapy depends on the severity of the illness, particularly the degree of edema.

### 14.4 Boils, furuncles, and carbuncles

**Acute boils, furuncles, and carbuncles**

Furuncles (or "boils") are infections of the hair follicle with suppuration that extends through the dermis into the subcutaneous tissue, forming a small abscess. Furuncles differ from folliculitis, in which inflammation is more superficial and pus is present in the epidermis. Furuncles or boils can occur anywhere on hairy skin. When infection extends to involve several adjacent follicles, producing a coalescent inflammatory mass with
pus draining from multiple follicular orifices, the lesion is called a carbuncle. Carbuncles tend to develop on the back of the neck and are especially likely to occur in diabetic persons. Boils and carbuncles are usually caused by *S. aureus*, although *Streptococcus pyogenes* can also be a cause. The isolation of a pure growth of an unusual organism, such as *E. coli* or *Pseudomonas*, from a child’s boil should prompt consideration of chronic granulomatous disease (CGD).^{21}

Outbreaks of furunculosis caused by *S. aureus* (methicillin-sensitive or MRSA) can occur in families and other settings such as sports teams. Inadequate personal hygiene and close contact with others with furuncles are important risk factors. In some cases, fomites may harbor the organism and facilitate transmission. Recommendations to control outbreaks include bathing with antibacterial soaps, such as chlorhexidine; thorough laundering of clothing, towels, and bed wear; separate use of towels and washcloths; and attempted eradication of staphylococcal carriage among colonized persons (see p. 228).^{1}

Small lesions may be treated with drainage alone. For large lesions, in addition to surgical incision and drainage, we recommend:

- **di/fluc/oxacillin** 12.5 mg/kg (max 500 mg) orally, 6-hourly for 5 days  OR  
- **cephalexin** 25 mg/kg (max 1 g) orally, 8-hourly for 5 days

For patients with anaphylactic penicillin allergy and for patients where community-associated methicillin-resistant *S. aureus* (cMRSA) is suspected because of ethnic background or local epidemiology, we recommend:

- **clindamycin** 10 mg/kg (max 450 mg) orally, 8-hourly for 5 days

The boil or furuncle should be lanced, if possible, and ongoing treatment should be based on culture and susceptibility.

**Recurrent furunculosis (recurrent boils)**

Some children have recurrent attacks of furunculosis. Most of these children have no demonstrable immune deficiency, and they and their family are well prior to onset.^{22–24} Other family members often have boils before or after the child, which may be because some strains are more virulent but may also suggest a familial tendency to boils. Recurrent furunculosis is strongly associated with eczema, because the skin excoriation is a focus for infection.^{22–24} Rare but important associations are diseases with defective neutrophil function, such as CGD^{21} and hyper-IgE syndrome (Job syndrome). An association has been described with low serum iron,^{25} but there are no studies showing that correcting iron deficiency improves furunculosis. For most children, the only identifiable predisposing factor is the presence of *S. aureus* in the anterior nares or, occasionally, elsewhere, such as the perineum.^{22} The prevalence of nasal staphylococcal colonization in the general population is 20–40%, but why some carriers develop recurrent skin infections and others do not is unclear.^{1}

We recommend taking swabs from any boils and from the nose to identify the organism and sensitivities, a nitroblue tetrazolium test or equivalent to exclude CGD, and a serum IgE if clinically indicated. More sophisticated neutrophil function tests are not widely available and not usually indicated.

**Question**  |  For children with recurrent furunculosis, do topical or oral antibiotics compared with no antibiotics reduce the frequency of recurrences?

**Literature review**  |  We found one RCT of nasal mupirocin^{26} and two RCTs of oral antibiotics^{27,28} for furunculosis due to methicillin-sensitive *S. aureus*. We found six RCTs and a Cochrane review^{29} for MRSA.

**Recurrent furunculosis with methicillin-sensitive *Staphylococcus aureus***

We found one RCT of 34 immunocompetent subjects with recurrent skin infections, who were carriers of methicillin-sensitive *S. aureus*.^{26} After an initial 5-day course of twice daily nasal mupirocin ointment for all patients, 17 patients continued to apply a 5-day course of nasal mupirocin every month for 1 year, and the other 17 patients applied a placebo ointment. The overall numbers of skin infections were 26 in the mupirocin group and 62 in the placebo group (p < 0.002). Colonization was eradicated in 8 of the 17 mupirocin-treated patients but only 2 of the placebo group. One of the 10 patients free of colonization during the 12-month treatment period had skin infections, but all 24 patients with positive cultures had boils (p < 0.01). Staphylococci resistant to mupirocin were
observed in 1 patient. No adverse effects of mupirocin were reported.26

The efficacy of nine different antibiotics used in different non-randomized regimens for eradicating nasal colonization with methicillin-sensitive S. aureus was investigated in a retrospective study. Clindamycin and ofloxacin were the most effective.30 In an RCT, 22 otherwise healthy adults with recurrent furunculosis were randomized to low-dose (150 mg/day) oral clindamycin or placebo.27 Seven of 11 placebo-treated patients (64%) but only 2 of 11 in the clindamycin group (18%) had a recurrent abscess within 3 months.27 Six of the 9 patients who responded to clindamycin treatment did not have a recurrent infection for at least 9 months after discontinuing antibiotic therapy. All patients tolerated the regimen without side effects.27 Rifampin has good tissue penetration, and even a short course might be useful to eradicate colonization. In an RCT, the addition of rifampin (rifampicin) to ofloxacin (or to vancomycin for MRSA) significantly improved cure from staphylococcal infections.28 The study did not look at colonization.28 Two observational studies suggested that a short course of rifampin, either alone31 or in combination with another antistaphylococcal antibiotics,32 could eradicate colonization and prevent recurrent boils in 50% or more of patients.

For patients with recurrent staphylococcal skin infections due to methicillin-sensitive S. aureus, we recommend treating any acute furuncles (see Section 14.4, p. 226). We then recommend using nasal mupirocin:

mupirocin 2% nasal ointment intranasally, 2 times daily for 5 days, and repeated monthly for 1 year

We recommend treating symptomatic household contacts in the same way as the index child. Some would recommend giving topical mupirocin to all household carriers, even if they were asymptomatic, to try to eradicate the organism.

Some authorities also recommend hygiene measures, such as washing daily with an antiseptic wash or soap containing triclosan 1% or chlorhexidine 2%, paying particular attention to hair-bearing areas, for at least 5 days, and washing clothes, towels, and sheets in hot water on two separate occasions.10 There is no evidence to back these recommendations.

Because of ease of administration and although there is only weak evidence from observational studies31,32 a short course of oral antibiotics is often more acceptable than nasal mupirocin, or can be tried if mupirocin fails. We recommend:

rifampicin 10 mg/kg (max 600 mg) orally, daily for 7 days PLUS ONE OF
clindamycin 10 mg/kg (max 450 mg) orally, 8-hourly for 7 days OR
di/fluc/oxa/nafcillin 12.5 mg/kg (max 500 mg) orally, 6-hourly for 7 days OR
cephalexin 25 mg/kg (max 1 g) orally, 8-hourly for 7 days

If lesions continue to recur despite good compliance, we recommend:

clindamycin 4 mg/kg (max 150 mg) orally, daily for 3 months

Recurrent furunculosis with MRSA
MRSA is more difficult to eradicate than methicillin-sensitive S. aureus. A Cochrane meta-analysis of six trials (384 participants) found no evidence that topical or systemic antibiotics, including mupirocin, were effective in eradicating MRSA nasal colonization.29

For MRSA, we do not recommend mupirocin. We recommend that ensuring the isolate is susceptible to the drug or drugs used in any oral antibiotic regimen. MRSA will be resistant to di/fluc/oxa/ nafcillin, but may be sensitive to other antibiotics including clindamycin, fusidic acid, or trimethoprim/sulfamethoxazole.

14.5 Cellulitis
Cellulitis is a diffuse, spreading skin infection, and the term excludes infections associated with underlying suppurative foci, such as cutaneous abscesses, necrotizing fasciitis (NF), septic arthritis, and osteomyelitis.1 The spreading, tender erythema may be associated with one or more of fever, lymphangitis, lymphadenopathy, and systemic toxicity. As the rash progresses, blistering may occur.1 The causative organism in spontaneous, rapidly spreading cellulitis is almost always S. pyogenes. Wound-associated purulent cellulitis is more likely to be associated with S. aureus. Haemophilus influenzae type b (Hib) was an important cause of facial cellulitis
(particularly, periorbital or buccal) in children <4 years old, but has disappeared in countries that routinely immunize against Hib, although may still be important in countries that do not.

Erysipelas is a severe form of cellulitis distinguished clinically by the following two features: the lesions are raised above the level of the surrounding skin, and there is a clear line of demarcation between involved and uninvolved tissue. Erysipelas is almost always caused by beta-hemolytic streptococci, usually group A (S. pyogenes), although similar lesions can be caused by serogroup C or G streptococci. Rarely, group B streptococci or S. aureus may be the cause.

Swartz gives an extensive differential diagnosis for cellulitis. The conditions in childhood that cause the most problem clinically are missing an underlying osteomyelitis or NF. It may require a bone scan or other imaging to exclude osteomyelitis (see Chapter 11). Ultrasound and/or magnetic resonance imaging (MRI) scan can help decide whether there is NF (see Section 14.9, p. 231).

**Antibiotic treatment of cellulitis and erysipelas**

We could find only five RCTs of antibiotic treatment of cellulitis, and no antibiotic was clearly superior to any other. Blood cultures are positive in only 4% of adult patients, and serology is rarely back quickly enough to guide therapy.

For oral therapy, to treat *S. pyogenes* or *S. aureus*, we recommend:

- **di/fluc/oxa/nafcillin 12.5 mg/kg (max 500 mg) orally, 6-hourly for 7–10 days** OR
- **cephalexin 25 mg/kg (max 1 g) orally, 8-hourly for 7–10 days** OR, if cMRSA likely,
- **clindamycin 10 mg/kg (max 450 mg) orally, 8-hourly for 7 days**

If *S. pyogenes* is confirmed, or suspected due to clinical presentation or local disease patterns, e.g. in some indigenous communities, we recommend:

- **phenoxymethylpenicillin 10 mg/kg (max 500 mg) orally, 6-hourly for 10 days** OR
- **cephalexin 25 mg/kg (max 1 g) orally, 8-hourly for 7–10 days** OR
- **procaine penicillin 50 mg (80,000 U)/kg (max 1.5 g or 2.4 million U) IM, daily for at least 3 days**

For patients with anaphylactic penicillin allergy, we recommend:

- **clindamycin 10 mg/kg (max 450 mg) orally, 8-hourly for 7 days**

It should be noted that the erythema may be slow to resolve and may even progress for the first 24–48 hours, even as the child becomes afebrile and improves. It is reassuring if the erythema is somewhat less intense at this time and starts to clear centrally.

For severe cellulitis with significant systemic features, or if the patient is not responding to oral therapy after 48 hours, we recommend commencing IV therapy and continuing IV until the patient is afebrile and the erythematous rash has improved. This may take anything from 2 days to 2 weeks. The patient can then change to oral therapy (as above for cellulitis and erysipelas).

To treat infection with either streptococci or staphylococci, we recommend:

- **di/fluc/oxa/nafcillin 50 mg/kg (max 2 g) IV, 6-hourly** OR
- **cephazolin 50 mg/kg (max 2 g) IV, 8-hourly** OR
- **cephalothin 2 g 50 mg/kg (max 2 g) IV, 6-hourly**

For patients with anaphylactic penicillin allergy and for patients where cMRSA is suspected because of ethnic background or local epidemiology (see p. 188), we recommend:

- **clindamycin 10 mg/kg (max 400 mg) IV, 8-hourly** OR
- **vancomycin <12 years: 30 mg/kg (max 1 g) IV, 12-hourly; 12 years and older: 25 mg/kg (max 1 g) IV, 12-hourly**

If there is significant systemic toxicity, consider the possibility of underlying myonecrosis or NF (see Section 14.9, p. 231).

### 14.6 Cutaneous larva migrans

The larvae of the dog and cat hookworms, *Ancylostoma braziliense* and *Agropyron caninum*, can cause a skin eruption in humans, called cutaneous larva migrans. This is different from visceral larva migrans and abdominal larva migrans, both of which are caused by *Toxocara*, the roundworms of dogs and cats. Human hookworms, *A. duodenale* and *Necator americanus*, can
cause local pruritus and a different, papulo-vesicular rash lasting 1–2 weeks at the site of entry, usually the feet.

After penetrating the epidermis, the dog or cat hookworm larva is unable to enter the bloodstream or lymphatics, and instead burrows just below the corium, traveling up to an inch a day. Papules mark the site of entry and advancing end of the larva, and the tunneling larva causes slightly elevated, red, serpiginous wavy lines that are intensely itchy. Vesicles may form along the course of the tunnels, and scaling develops as the lesions age. The most common sites in children are the buttocks and the dorsum of the feet, but any area can be affected. The eruption generally disappears after 1–2 months, but may persist for 6 months or longer. Diagnosis is clinical. Biopsy may show an inflammatory, eosinophilic infiltrate but not the parasite, while serologic assays are available only in research laboratories.

There are no controlled trials of therapy, but observational studies favor topical treatment. Larvae can be eliminated in >95% of cases with topical 15% thiabendazole, which can be easily made from the oral preparation, if not commercially available, by crushing 500-mg tablets in a water-soluble base.\textsuperscript{36,37} We recommend:

**thiabendazole 15% cream, topically, 8–12-hourly for 5–10 days**

Oral treatment may be needed for children who do not respond or who relapse. Both ivermectin and albendazole are very effective,\textsuperscript{38} but children are less likely to relapse after treatment with ivermectin.\textsuperscript{38} We recommend:

**ivermectin (children >5 years) 200 µg/kg orally, as a single dose** OR
**albendazole 400 mg (children <10 kg: 200 mg) orally, daily for 3 days**

Cryotherapy is painful and has an unacceptably high failure rate.\textsuperscript{36,39}

### 14.7 Folliculitis

Folliculitis is inflammation of the hair follicles due to an infection or irritation in which the inflammation is more superficial than in a furuncle or boil and pus is present in the epidermis.\textsuperscript{1}

Folliculitis is most often due to *S. aureus* infection, but this should be confirmed by culture, as the condition can also be caused by *Pseudomonas aeruginosa* (usually from hot tubs or spas),\textsuperscript{40–42} yeasts like Malassezia,\textsuperscript{43} and viruses like herpes simplex virus or varicella-zoster virus.\textsuperscript{44} A non-infective variant known as eosinophilic folliculitis can occur in HIV infection.\textsuperscript{45}

Staphylococcal infection can be treated as for staphylococcal impetigo (see Section 14.8, below). If skin swabs grow *P. aeruginosa*, the most important treatment measure is to identify the source and cease contact until the water supply has been treated\textsuperscript{41,42}.

### 14.8 Impetigo

In affluent communities, impetigo is most commonly caused by *S. aureus* and less commonly by *S. pyogenes* (group A streptococcus), although sometimes both organisms occur together. *S. pyogenes* is usually the primary pathogen in disadvantaged circumstances, such as remote Australian indigenous communities, and causes non-bullous or crusted impetigo, characterized by yellow, crusting lesions. It may be associated with scabies, and complications include glomerulonephritis (see Chapter 17) and rheumatic fever (see Chapter 3). Bullous impetigo, which causes round, itchy blisters, is caused by *S. aureus*.

Impetigo is mainly a disease of young children, but may be seen at any age. The condition is contagious and can spread from person to person in child care facilities, in schools, and in crowded, underprivileged communities.\textsuperscript{46}

We found a Cochrane review\textsuperscript{46} and also a non-Cochrane systematic review\textsuperscript{47} of treatment of impetigo. Both found that topical antibiotics were at least as good as oral antibiotics at curing impetigo, and that topical mupirocin was better than oral erythromycin.\textsuperscript{46,47} Also, there was no significant difference between different topical agents, including mupirocin and fusidic acid.\textsuperscript{46,47} The Cochrane review found that oral penicillin was not as effective as most other antibiotics, but included studies of patients with impetigo due to *S. aureus* as well as *S. pyogenes*.\textsuperscript{46}

If cultures are not back, it seems reasonable in settings other than remote communities to use a regimen that will treat both *S. aureus* and *S. pyogenes*. For mild or localized infections, we recommend:

**mupirocin 2% topically, 8-hourly**
For widespread or recurrent infections, cephalaxin and dicloxacillin are equally effective. We recommend:

- **cephalexin** 12.5 mg/kg (max 250 mg) orally, 6-hourly
- **dicloxacillin** 12.5 mg/kg (max 250 mg) orally, 6-hourly

For patients with anaphylactic penicillin allergy and for patients where cMRSA is suspected because of ethnic background (see p. 188) or is proven, we recommend:

- **clindamycin** 10 mg/kg (max 450 mg) orally, 8-hourly for 5 days

In situations where *S. pyogenes* is highly likely, and there is a relatively high risk of major complications like glomerulonephritis and rheumatic fever, such as in indigenous communities, we recommend:

- **phenoxymethylpenicillin** 10 mg/kg (max 500 mg) orally, 6-hourly OR
- **benzathine penicillin** 900 mg = 1.2 million units (children 3 to <6 kg: 225 mg; 6 to <10 kg: 337.5 mg; 10 to <15 kg: 450 mg; 15 to <20 kg: 675 mg) IM, as a single dose

With recurrent or resistant impetigo, chronic carriage of *S. aureus* is possible. We recommend taking swabs from the nose and/or perineum, depending on the location of the impetigo. If swabs are positive, consider treating the whole family and close contacts (see pp. 227–8).

**14.9 Necrotizing skin and soft tissue infections**

**Diagnosis: distinguishing necrotizing skin and soft tissue infections from cellulitis**

Necrotizing skin and soft tissue infections tend to be deeper than other skin infections like cellulitis and may involve the fascial and/or muscle compartments. They cause major destruction of tissue and can be fatal. Critical ill patients with skin and soft tissue infections may have underlying necrosis of the soft tissues (NF) or muscle (myonecrosis). Extensive necrosis is referred to as gangrene.

Infection can develop from an initial break in the skin related to trauma or surgery, and can involve just one organism (usually *S. pyogenes*, or more rarely *Clostridium perfringens* causing gas gangrene or *S. aureus*, including MRSA) or can be polymicrobial (usually mixed aerobic and anaerobic bacteria). Penetrating and crush injuries are particularly likely to cause these infections, but life-threatening *S. pyogenes* NF can occur spontaneously or following varicella (chicken pox).

A number of syndromes of necrotizing soft tissue infections have been described on the basis of etiology, microbiology, and anatomic location, but there is a common initial approach in terms of the diagnosis, antimicrobial treatment, and decision to use operative management. The initial concern is usually to distinguish between cellulitis and a necrotizing infection. The clinical features that suggest the presence of a necrotizing infection are described in reviews and shown in Box 14.1.

What is the evidence that these clinical criteria truly distinguish necrotizing infection from cellulitis (with histologic proof as the “gold standard”)? A North American surgical team developed a model from a comparison between proven NF patients and matched

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**Box 14.1 Clinical features described as suggestive of a necrotizing skin and soft tissue infection.**

- Pain: severe and constant
- *Bullae*
- *Purple skin discoloration (sometimes described as ecchymosis or bruising)*
- Skin necrosis
- Gas in the soft tissues (palpable crepitus or gas on radiograph)
- *Edema extending beyond the margin of erythema*
- *Cutaneous anesthesia*
- Systemic toxicity; e.g., high fever, hypotension, shock, and delirium
- Rapid spread
- *Denotes clinical features shown to be more common in necrotizing infection than in cellulitis.*
non-NF controls.\textsuperscript{52} They then used the model to compare retrospectively 31 NF patients with 328 non-NF patients.\textsuperscript{51} NF patients had a significantly lower mean admission systolic BP (124 mm Hg versus 136 mm Hg, \( p = 0.007 \)) and higher mean admission respiratory rate (20 versus 18 breaths per minute, \( p = 0.009 \)), but no significant difference in temperature or heart rate. Two NF patients (7\%) and 2 non-NF patients (1\%) presented with hypotension (SBP <90 mm Hg, \( p = \text{NS} \)). No threshold for any vital sign significantly distinguished NF from non-NF patients.

Physical examination of both NF and non-NF patients revealed a combination of tenderness, erythema, warmth, swelling, and fluctuance. NF patients differed from non-NF patients with respect to the presence of tense edema (23\% versus 3\%, \( p = 0.0002 \)), bullae (16\% versus 3\%, \( p = 0.006 \)), purplish skin discoloration (10\% versus 1\%, \( p = 0.02 \)), and sensory or motor deficit (13\% versus 3\%, \( p = 0.03 \)). Skin necrosis was present in 6\% of NF patients and 2\% of non-NF patients (\( p = \text{NS} \)). Seven of 22 NF patients (32\%) had gas on plain radiograph, versus 6 of 224 non-NF patients (3\%) (\( p < 0.0001 \)). No patient had crepitus, so radiographic evidence of gas was present in about a third of patients, but no clinical evidence of gas. This study did not look at pain severity.\textsuperscript{51}

Laboratory criteria may help distinguish NF from non-NF patients. A retrospective study compared laboratory results in 145 NF patients with 309 patients with severe cellulitis or abscesses. A score based on total white cell count, hemoglobin, sodium, glucose, serum creatinine, and C-reactive protein had good positive and negative predictive value in this population, although may not be so useful in clinical practice, as the results are likely to be abnormal in severe cellulitis.\textsuperscript{53} The serum creatine phosphokinase (creatinine kinase, CK) is rarely raised in cellulitis in contrast to NF: in one series, 5\% of patients with erysipelas had a serum CK >600 IU/L.\textsuperscript{54} In another series,\textsuperscript{55} serum CK was >200 IU/L in 75\% of patients with group A streptococcal NF and >600 IU/L in 61\%. However, in the same study,\textsuperscript{55} serum CK was >200 IU/L in 26\% of patients with NF due to other organisms, and none of these had a CK >600 IU/L. Patients with group A streptococcal NF had a higher mortality. An elevated CK is, therefore, useful for supporting a diagnosis of NS, particularly group A streptococcal NF, but a normal CK does not exclude the diagnosis.

Can imaging reliably differentiate between cellulitis and NF? Computed tomography (CT) scan, ultrasound, and MRI for the imaging of necrotizing soft tissue infection have been intensely studied and reviewed.\textsuperscript{56} Authors have reported features that they consider to be indicative of NF, but these are difficult to verify objectively. MRI is probably the most sensitive modality, but its sensitivity often exceeds its specificity, resulting in overestimation of the extent of deep fascial involvement.\textsuperscript{56} However, absence of deep fascial involvement on MRI effectively excludes NF. While imaging can be an invaluable adjunct to diagnosis, it may not be readily available and is certainly not cheap. In patients with a suspicion of NF, operative debridement should not be delayed while waiting for an MRI scan.

**Treatment of necrotizing skin and soft tissue infections**

**Surgery for necrotizing skin and soft tissue infections**

The principle of treatment is a combination of surgical removal of necrotic tissue and early antibiotics.\textsuperscript{57} We could find 156 review articles on surgery for NF, but not surprisingly no RCTs.

**Antibiotics for necrotizing skin and soft tissue infections**

The recommended antibiotic treatment of choice for group A streptococcal and for clostridial necrotizing infections is clindamycin plus penicillin.\textsuperscript{1} This recommendation is based on susceptibility but not on clinical trials.

For *S. pyogenes* NF, or for proven clostridial infection, we recommend:

- benzylpenicillin 60 mg (100,000 U)/kg (max 2.4 g or 4 million U) IV, 4-hourly PLUS
- clindamycin 15 mg/kg (max 600 mg) IV, 8-hourly

For empiric therapy, meropenem is used until Gram-negative organisms have been excluded. We recommend:

- clindamycin 15 mg/kg (max 600 mg) IV, 8-hourly PLUS
- meropenem 25 mg/kg (max 1 g) IV, 8-hourly
Although penicillin is often added, this is not likely to improve the efficacy of the above regimen, so we do not recommend it.

**Intravenous immunoglobulin for necrotizing skin and soft tissue infections**

Intravenous immunoglobulin (IVIG) contains antibodies against streptococcal superantigens, and although IVIG has been used in patients with severe streptococcal infections, there have been no RCTs of the use in streptococcal toxic shock or NF. Reports have been case reports, uncontrolled case series, or have used historic controls. Recommendations to use or to consider using IVIG are based on the severity of the illness, the difficulty in doing RCTs (so there is a lack of evidence of efficacy rather than evidence of lack of efficacy), and the likelihood that benefit will outweigh harm. If used, the recommended dose is:

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normal immunoglobulin 1–2 g/kg IV, repeated on days 2 and 3 if indicated
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**Hyperbaric oxygen for necrotizing skin and soft tissue infections**

A review found seven studies reporting the results of hyperbaric oxygen in the treatment of necrotizing skin and soft tissue infections; all the studies were uncontrolled, retrospective, and observational studies. The review concluded that the results were inconsistent, with some studies claiming that hyperbaric oxygen can improve patient survival and decrease the number of debridements required to achieve wound control, whereas others failed to show any beneficial effect.

We found 19 RCTs, a 2001 Cochrane review, and treatment guidelines, but one of the major problems was whether the findings are applicable when there is resistance to pediculicides. The Cochrane review found only four eligible studies and found that pediculicides were effective compared with no treatment, but did not favor any one pediculicide.

The emergence of pediculicide resistance has driven studies of physical methods of lice removal, particularly using fine tooth combs. We found four RCTs comparing wet combing with conditioner. Two studies strongly found that wet combing using fine tooth combs and conditioner (“Bug Busting”) was far more effective than using a pediculicide. In contrast, one RCT found that wet combing was less effective than a pediculicide and another found that adding wet combing to a pediculicide did not improve eradication.

Because it is safe, cheap, and often effective, and avoids the risk of resistance and toxicity from using pediculicides, we recommend wet combing plus conditioner as the initial treatment of choice for head lice.

### 14.11 Perianal cellulitis

Perianal cellulitis has been recognized to be caused commonly by group A beta-hemolytic streptococci for many years, although other reported causes include *S. aureus*, pinworms, and polymicrobial synergistic gangrene in immunocompromised children. Streptococcal perianal cellulitis occurs mainly in children ages 6 months to 10 years. It causes sharply circumscribed perianal erythema, with or without itching, anal fissures, pain on defecation, constipation, rectal bleeding, and mucopurulent anal discharge.

The disorder can be associated with guttate psoriasis and with vulvovaginitis in prepubertal girls (see Section 13.2, p. 211), and with balanoposthitis in boys (see Section 13.1, p. 211). Infection sometimes spreads in families or in day care.

Treatment of perianal streptococcal cellulitis has never been prospectively evaluated. Effective treatment of sporadic cases with oral penicillin, erythromycin, or mupirocin cream alone has been reported, but recurrence rates may be as high as 40–50%.

**14.10 Pediculosis capitis (head lice)**

Pediculosis capitis or infestation with head lice is extremely common in child care and schools throughout the world. One of the major problems with control has been the emergence of resistance to pediculicides, such as permethrin and malathion.

**Question** | For children with head lice, are topical pediculicides compared with wet combing compared with no treatment or placebo effective at eradicating head lice?

**Literature review** | We found 19 RCTs and a Cochrane review of interventions for head lice.
We recommend:

**phenoxymethylpenicillin (penicillin V) 10 mg/kg (max 500 mg) orally, 6-hourly**

### 14.12 Pyomyositis

Pyomyositis is the presence of pus within individual muscle groups.\(^{83–86}\) Local muscle trauma is thought to predispose to pyomyositis, but a clear history of trauma is often not obtained. Because it is most commonly reported in the tropics, this condition is often called tropical pyomyositis,\(^{83}\) but cases are also reported in temperate climates, often in children without underlying risk factors.\(^{84–86}\)

The most common organism by far in both tropical and temperate settings is *S. aureus*,\(^{83–86}\) which can be methicillin-sensitive or methicillin-resistant (often cMRSA).\(^{83}\) Occasionally, *S. pneumoniae* or a Gram-negative enteric bacillus is responsible.\(^{83–86}\) Blood culture results are positive in 5–30% of cases.\(^{83–86}\)

Children usually present with pain in a single muscle or muscle group, muscle spasm, and fever, although occasionally the presentation is more indolent, with fever but little pain.\(^{81–83}\) The disease most often occurs in an extremity, but any muscle group can be involved, including the psoas or trunk muscles. An iliopsoas abscess classically presents with hip pain and difficulty walking, which mimics septic arthritis, although children with iliopsoas abscess tend to hold the hip rigid, while children with septic arthritis hold it flexed in the neutral position.\(^{87}\)

Pyomyositis may coexist with septic arthritis and/or osteomyelitis (see Chapter 11). The diagnosis of pyomyositis can be made with ultrasound, CT, or MRI scan, which will delineate the extent of the lesion and whether or not there is also septic arthritis.

Ultrasound- or CT-guided percutaneous drainage can be both therapeutic and diagnostic.\(^{83–86}\)

For empiric therapy, in the absence of any other indications, we recommend:

**clindamycin 10 mg/kg (max 450 mg) IV, 8-hourly**

- THEN (if susceptible)
  - **vancomycin <12 years: 30 mg/kg (max 1 g); 12 years and older: 25 mg/kg (max 1 g) IV, 12-hourly**

If *S. aureus* is not susceptible to macrolides, and patient is allergic to penicillin, base oral therapy following vancomycin on proven susceptibility. Suitable oral options may be trimethoprim+sulfamethoxazole or doxycycline.

### 14.13 Scabies

Scabies is a common parasitic infection caused by the mite *Sarcoptes scabiei* variety *hominis*. The worldwide prevalence may be as high as 300 million cases yearly.\(^{88,89}\) Scabies is spread by close physical contact between infected persons. Human scabies is not acquired from animals. Scabies occurs in both sexes, at all ages, in all ethnic groups, and at all socioeconomic levels. In an epidemiologic study in the UK, scabies was more prevalent in urban areas, among women and children, and in winter.\(^{66}\)

Scabies causes itchy, linear, or serpiginous lesions with burrows. In infants, the eruption may be more vesicular, and can occur on the head, neck, palms, and soles, as well as elsewhere on the body and limbs. In older children and adults, lesions are more often confined to the interdigital spaces, wrists, elbows, axilla, areolae, waist, umbilicus, thighs, buttocks, and genitalia.\(^{88,90}\) However, scabies can occur above the neck in elderly and in malnourished persons. Lesions can become secondarily infected, leading to pyoderma or impetigo.

A crusted form of scabies called Norwegian scabies can occur in immunocompromised persons, including those with congenital immune deficiency or HIV infection.\(^{91,92}\) In crusted (Norwegian) scabies, the mite population on the patient is very high due to a poor host response.

The diagnosis of scabies is primarily clinical.\(^{88,91}\) In a report from a sub-Saharan region with a high
prevalence of scabies (13%), the presence of diffuse itching and visible lesions associated with either at least two typical locations of scabies or a household member with itching had 100% sensitivity and 97% specificity for the diagnosis. Diagnostic tests involve skin scraping with a blade or biopsy, but have a relatively low sensitivity. Empiric treatment is reasonable for patients with classical clinical findings. However, empiric treatment is not recommended for persons with generalized itching, even after exposure (e.g., staff), unless they have a typical eruption.

Topical treatment for scabies
Permethrin and lindane are the two most studied topical treatments for scabies. A Cochrane review found four randomized trials comparing these agents. A single overnight application of permethrin was found to be more effective than lindane and less toxic. However, there was considerable heterogeneity among studies in the meta-analysis, and a different author examined the same data and concluded that if clinical cure was the outcome, there was no significant treatment advantage for permethrin.

Reversible neurotoxicity has been described following an overdose of topical lindane, and the potential of lindane for neurotoxicity, especially if giving repeated applications, has caused sufficient concern that the product is no longer available in the UK or Australia. Although it costs more than lindane, 5% permethrin is recommended by the Centers for Disease Control and Prevention as first-line topical therapy for scabies. Mass treatment with permethrin has also been effective in controlling scabies in communities in which it is endemic.

Other topical treatments include benzyl benzoate (not available in the USA) and crotamiton. Limited data from an RCT suggest that crotamiton is less effective after 4 weeks than permethrin (61% versus 89% cure). In Vanuatu, in the South Pacific, where scabies is a major public health problem, 10% benzyl benzoate was as effective as a single oral dose of ivermectin (51% versus 56%) but more likely to cause burning or stinging (33% versus 7%). In France, where permethrin is not available, benzyl benzoate is considered first-line local treatment, mainly on the basis of professional experience. The Cochrane review concluded that data were insufficient to compare the effectiveness of either benzyl benzoate or crotamiton with lindane or permethrin.

There are insufficient data to recommend sulfur, topica ivermectin, or tea tree oil, which have been suggested as treatments. Pyrethrin aerosol spray, which has been used to treat scabies, can cause severe and even fatal asthma.

For the topical treatment of scabies, permethrin 5% cream is at least as effective as other agents, safer, and cheaper. Benzyl benzoate is effective in scabies if used correctly, but it is more irritating than is permethrin. We recommend:

- **Permethrin 5% cream (adult and child >6 month)** topically; leave on the skin for 8–14 hours (usually overnight) and reapply to hands if they are washed
- **Benzyl benzoate 25% emulsion (child <2 years):** dilute with 3 parts of water; child 2–12 years: dilute with equal parts of water) topically; leave on the skin for 24 hours and reapply to hands if they are washed

A second dose 1 week later improves cure rate.

If secondary bacterial infection is present, also treat for impetigo (see Section 14.9).

Treatment of scabies in babies
The recommended treatment of scabies in babies is:

- **Permethrin 5% cream** topically to the entire skin surface; include scalp, avoid eyes and mouth, cover hands in mittens to avoid the child ingesting the medication, leave on for 8 hours

Although there are limited safety data on permethrin in babies <6 months old, this must be balanced against the high morbidity of untreated scabies. If the clinician judges the risks of treatment with permethrin to outweigh the benefit, alternatives are:

- **Sulfur 10% in white soft paraffin** topically, daily for 2–3 days (child <2 months: sulfur 5% in white soft paraffin) OR
- **Crotamiton 10% cream** topically, daily for 2–3 days

Oral treatment for scabies
Topical treatments may cause local reactions, especially when the skin is excoriated or eczematous, and there
is a potential risk from percutaneous absorption. Oral ivermectin is an alternative.\textsuperscript{100} Several controlled trials have assessed the efficacy of a single dose of ivermectin (200 μg/kg) for the treatment of scabies. Ivermectin is superior to placebo (74\% versus 15\% cure).\textsuperscript{101} In small studies, no significant differences in clinical cure rates were found between ivermectin and 10\% benzyl benzoate,\textsuperscript{98} or between ivermectin and lindane.\textsuperscript{102} In one RCT,\textsuperscript{103} a single dose of oral ivermectin was less effective (70\% cure) than a single overnight application of 5\% permethrin (98\% cure), but a second dose of ivermectin 2 weeks later increased the cure rate to 95\%. The lower efficacy of single-dose ivermectin could reflect the lack of ovicidal action of the drug.

Ivermectin is potentially neurotoxic and costly. No serious adverse effects were noted in a program of mass treatment with ivermectin for children with scabies in the Solomon Islands.\textsuperscript{104} However, encephalopathy has been reported in heavily infected patients with onchocerciasis, who are treated with ivermectin.\textsuperscript{105} One study reported an excess risk of death among elderly patients who received ivermectin for scabies,\textsuperscript{106} but this observation has not been confirmed in other studies, including studies of nursing home residents.\textsuperscript{107}

**Treatment of crusted (Norwegian) scabies**

There are no RCTs of the treatment of crusted (Norwegian) scabies, and the optimum treatment is uncertain.\textsuperscript{108} A retrospective study using historic controls found that the mortality from Norwegian scabies in Northern Australia fell from 4.3 to 1.1\%, coincident with but not necessarily because of the introduction of multiple dosing with oral ivermectin.\textsuperscript{88} The following recommendations are empiric.\textsuperscript{63} Ivermectin therapy is effective and should be given in association with more frequent scabicide dosing, but is not recommended in children <5 years of age. To reduce scaling, topical keratolytics (e.g., salicylic acid 5–10\% in sorboline cream, or lactic acid 5\% plus urea 10\% in sorboline cream) can be applied daily after washing on days when scabicides are not applied.\textsuperscript{63}

For less severe crusted scabies, we recommend:

**Ivermectin 200 μg/kg (child >5 years) orally, as single doses 1 week apart**

For moderate crusted scabies, use:

**Ivermectin 200 μg/kg (child >5 years) orally, on days 1, 2, and 8 (i.e., three single doses)**

For severe crusted scabies, use:

**Ivermectin 200 μg/kg (child >5 years) orally, on days 1, 2, 8, 9, and 15 (i.e., five single doses), with two further doses on days 22 and 29 for extremely severe cases**

Scabies in HIV-infected individuals may be resistant to repeated attempts at topical therapy.\textsuperscript{109} There are no RCTs, and advice is empiric.\textsuperscript{63,109} We recommend:

**Ivermectin 200 μg/kg orally, weekly until scrapings are negative and there is no further clinical evidence of infestation**

**14.14 Water-related infections**

Wound infections, cellulitis, or sepsis associated with water, e.g. in fishermen, swimmers, or aquarium owners, may be associated with water-loving Gram-negative bacilli, including Vibrios, Aeromonas, Klebsiella, \textit{E. coli}, and anaerobes (see also Section 14.2, p. 226).\textsuperscript{110} There is little difference between the organisms following exposure to fresh water from a river, brackish water, or salt water, although \textit{Mycobacterium marinum} is particularly associated with fish tanks.\textsuperscript{111}

For empiric treatment, we recommend:

**Ciprofloxacin 10 mg/kg (max 500 mg) orally, 12-hourly**

or for systemic therapy:

**Cefotaxime 50 mg/kg (max 2 g) IV, 8-hourly** OR **Ciprofloxacin 10 mg/kg (max 400 mg) IV, 12-hourly**

**Coral cuts**

Coral cuts are often infected with \textit{S. pyogenes}, but infection may also occur with marine pathogens. For mild infection, we recommend treating as for impetigo (see Section 14.8, p. 230), and if unresponsive or severe, treating as for severe cellulitis (see p. 229), until culture results are back.

**Mycobacterium marinum infections**

\textit{M. marinum} causes a localized papular or nodular skin lesion associated with exposure to fresh water, often
from a fish tank or aquarium (“fish-tank granuloma” or “swimming-pool granuloma”). Diagnosis is often made by biopsy, and antibiotic therapy may not be required if a single lesion is successfully excised. There have been no controlled trials that compare the multiple treatment regimens for *M. marinum*, but a review of the literature suggested that treatment with two of clarithromycin, ethambutol, and rifampicin was most likely to be successful. It is suggested to treat for 1–2 months after the resolution of all lesions (typically 3–6 mo in total). We recommend:

- clarithromycin 12.5 mg/kg (max 500 mg) orally, 12-hourly PLUS EITHER
ethambutol 15 mg/kg (child ≥6 years) orally, daily OR rifampicin 10 mg/kg (max 600 mg) orally, daily

14.15 Wound infections

**Surgical site infections**

Post-operative surgical site infections may settle with drainage and cleaning. Cultures should be obtained. Topical antibiotics are not recommended because they can select for the emergence of resistant organisms and can cause skin reactions.

For mild-to-moderate infection with surrounding cellulitis, we recommend:

- di/flucl/oxa/nafcillin 12.5 mg/kg (max 500 mg) orally, 6-hourly OR cephalexin 12.5 mg/(max 500 mg) orally, 6-hourly

Alternatively, if Gram-negative organisms are suspected or known to be involved, we recommend:

- amoxycillin + clavulanate 22.5 + 3.2 mg/kg (max 875 + 125 mg) orally, 12-hourly

For more severe infections, particularly where systemic symptoms are present, we recommend:

- di/flucl/oxa/nafcillin 50 mg/kg (max 2 g) IV, 6-hourly OR cephalothin 50 mg/kg (max 2 g) IV, 6-hourly OR cephazolin 50 mg/kg (max 2 g) IV, 8-hourly

If Gram-negative organisms are suspected or known to be involved, we recommend adding:

- gentamicin 4–6 mg/kg (child <10 years: 7.5 mg/kg; ≥10 years: 6 mg/kg) IV, daily

Alternatively, it is possible to use a single preparation, which has advantages of ease of administration, but disadvantages of increased cost and probably increased risk of selecting for resistant organisms:

- piperacillin + tazobactam 100 + 12.5 mg/kg (max 4 + 0.5 g) IV, 8-hourly OR ticarcillin + clavulanate 50 + 1.7 mg/kg (max 3 + 0.1 g) IV, 6-hourly

If MRSA is proven (or suspected), or for patients with anaphylactic penicillin allergy, we recommend:

- vancomycin <12 years: 30 mg/kg (max 1 g); 12 years and older: 25 mg/kg (max 1 g) IV, 12-hourly

For subsequent oral therapy, see Section 14.12 pyomyositis.

**Wound infections related to vascular access**

Vascular-access devices are the most common iatrogenic factor predisposing patients to skin and soft tissue infections. Many patients with intravenous catheters have additional factors that increase their risk of infection, such as neutropenia or defects of cellular or humoral immunity. Intravenous vascular-access devices are almost universal for patients who are undergoing cancer therapy; for stem cell, marrow, and solid organ transplant recipients; and for intensive care patients. Many of these catheters remain in place for prolonged periods, and the risk of cutaneous infections varies with the device, the duration of catheter placement, and the severity of immune suppression.

Cutaneous infections associated with catheter placement include entry-site infections (inflammation from the entry site to the first subcutaneous cuff), tunnel infections (inflammation involving the skin and soft tissues surrounding the catheter tunnel from the catheter cuff to the venous entrance), or vascular port-pocket infections. Blood cultures are positive in 30–40% of tunnel and port-pocket infections, but rarely positive when catheter infection is limited to the entry site.

Gram-positive organisms cause two-thirds of all vascular device infections, particularly coagulase-negative staphylococci and *S. aureus*, but other causes include Gram-negative bacilli, fungi, and atypical mycobacteria. The prevalence of infection due to Gram-positive pathogens justifies recommending the use of empiric intravenous vancomycin for treatment
of clinically serious catheter-associated infections. Most entry-site infections can be treated effectively with appropriate antimicrobial therapy without catheter removal. It is recommended to remove the catheter in tunnel or port-pocket infections. Catheter-site infections caused by fungi or non-tuberculosis mycobacteria will not resolve without catheter removal and debridement of devitalized soft tissues. One case series reported cure of all tunnel infections caused by non-tuberculous mycobacteria, using combination antimicrobial therapy for 3–6 weeks plus catheter removal and debridement of the infected soft tissue.

Treatment should be based on cultures. For empiric therapy, pending culture results, we recommend:

vancomycin <12 years: 30 mg/kg (max 1 g); 12 years and older: 25 mg/kg (max 1 g) IV, 12-hourly

**Post-traumatic wound infections**

Antibiotics are often used in the early treatment of contaminated wounds following traumatic injuries, such as muscular, skeletal, and soft tissue trauma, crush injuries, penetrating injuries, and stab wounds. Careful cleaning and debridement of wounds is important to prevent infection, and immobilization and elevation reduce edema. The most common pathogens are *S. aureus*, *S. pyogenes*, *C. perfringens*, and aerobic Gram-negative bacilli. For penetrating foot injuries through footwear, *P. aeruginosa* is commonly implicated (see p. 157).

In all cases, a patient’s tetanus immunisation status should be assessed. For wounds caused by bites, see Section 14.1, p. 224.

**Clean wounds**

Antibiotics are not usually necessary for clean wounds. If it is decided to give empiric antibiotics to treat the above organisms, because management is delayed (≥8 hours) or debridement is difficult, we recommend:

- di/flucloxacillin 12.5 mg/kg (max 500 mg) orally, 6-hourly OR
- cephalexin 12.5 mg/(max 500 mg) orally, 6-hourly OR
- amoxicillin + clavulanate 22.5 + 3.2 mg/kg (max 875 + 125 mg) orally, 12-hourly

For patients with anaphylactic penicillin allergy, or if *Pseudomonas* infection is a risk, we recommend:

- ciprofloxacin 10 mg/kg (max 500 mg) orally, 12-hourly PLUS
- clindamycin 10 mg/kg (max 450 mg) orally, 8-hourly for 5 days

**Contaminated wounds**

For contaminated wounds, it is important to prevent gas gangrene due to clostridial infection. Metronidazole and clindamycin provide adequate prophylaxis. We recommend:

- di/flucloxacillin 50 mg/kg (max 2 g) IV, 6-hourly PLUS
- gentamicin 4–6 mg/kg (child <10 years: 7.5 mg/kg; ≥10 years: 6 mg/kg) IV, daily PLUS
- metronidazole 12.5 mg/kg (max 500 mg) IV, 12-hourly

Alternatively, use:

- metronidazole 12.5 mg/kg (max 500 mg) IV, 12-hourly PLUS EITHER
- cephalothin 50 mg/kg (max 2 g) IV, 6-hourly OR
- cephazolin 50 mg/kg (max 2 g) IV, 8-hourly

Another possibility is:

- clindamycin 15 mg/kg (max 600 mg) IV or orally, 8-hourly PLUS
- gentamicin 4–6 mg/kg (child <10 yr: 7.5 mg/kg; ≥10 years: 6 mg/kg) IV, daily

For subsequent oral therapy, use an oral regimen as for clean wounds (see above).

**References**

72 Meinking TL, Clineschmidt CM, Chen C et al. An observer-blinded study of 1% permethrin creme rinse with and
89 Walker GJA, Johnstone PW. Interventions for treating scabies. The Cochrane Database of Systematic Reviews 2000;(3);Art No CD000320.


Severe sepsis has been defined in adults and older children as the systemic response to an infection, as manifested by organ dysfunction, hypoperfusion, or hypotension, and two or more of fever, tachycardia, tachypnea, and elevated white cell count.¹ Consensus definitions of sepsis, severe sepsis, septic shock, and the systemic inflammatory response syndrome in neonates and children have been published.² Antibiotics to cover the most likely pathogens, sometimes loosely called “broad spectrum” antibiotics, are only one aspect of the management of septic shock. Other interventions to preserve tissue perfusion and oxygenation are given in Section 15.3, p. 245 and in Boxes 15.1 and 15.2.

15.1 Antibiotic therapy for severe sepsis

**Question** | For children with severe sepsis, is one antibiotic regimen more effective compared to other regimens in terms of mortality or morbidity?

**Literature review** | We reviewed 801 RCTs of sepsis or sepsis syndrome in children, but none compared antibiotic choices for immunocompetent children with severe sepsis, other than those comparing once daily with multiple dose aminoglycosides. We found one review.³

The choice of empiric antibiotics will be guided to an extent by the spectrum of organisms causing infection locally, and also by clinical criteria, such as the presence of rash or accompanying soft tissue infection. Nevertheless, it is surprising and disappointing how little published data are available on the antibiotic treatment of severe sepsis. We found a so-called “evidence-based” review, but because the review was severely limited by the small number of trials and absence of relevant RCTs, most of the recommendations were based on consensus.³ We found one RCT that found no difference between IV penicillin and IV ceftaxime in the empiric treatment of 154 children aged 3 months to 15 years, mostly with moderately severe infections such as pneumonia, other lower respiratory infections, and other common acute infections warranting hospitalization and parenteral antimicrobials.³ Our recommendations are, therefore, based on the organisms infecting children in epidemiologic studies of severe sepsis, but may need to be varied depending on local circumstances.

**Organism unknown, meningitis not excluded**

For empiric therapy of severe sepsis with no obvious source of infection in children 0–3 months of age, when meningitis has not been excluded, we recommend:

- amoxi/amoxicillin 50 mg/kg IV, 6-hourly PLUS cefotaxime 50 mg/kg IV, 6-hourly PLUS vancomycin 15 mg/kg IV, 6-hourly

This regimen provides effective treatment for the likely infant pathogens acquired through the respiratory route, such as *Haemophilus influenzae* type b, pneumococcus, and meningococcus, but also bowel/urinary-tract-derived pathogens such as *Escherichia coli* and other Gram-negative bacilli. Enterococci and Listeria, neonatally acquired organisms that can cause post-neonatal sepsis, are inherently resistant to cefotaxime, hence the use of ampicillin. Vancomycin is used because meningitis caused by strains of pneumococcus insensitive to penicillin does not respond adequately to ampicillin. Vancomycin also provides cover for MRSA infection, either community- or hospital-acquired, and should be used if there are risk factors, such as ethnicity, soft tissue infection, or prior colonization.

Children aged >3 months are more likely to be infected with *Staphylococcus aureus*, and an antistaphylococcal antibiotic is indicated. Recommended antibiotics are:

- di/fluc/oxa/nafcillin 50 mg/kg (max 2 g) IV, 6-hourly PLUS vancomycin 15 mg/kg (max 500 mg) IV, 6-hourly
Organism unknown, meningitis excluded
For empiric therapy of severe sepsis with no obvious source of infection in children 0–3 months of age when meningitis has been excluded, recommended antibiotics to cover respiratory and gastrointestinal or urinary tract pathogens are:

- amoxi/ampicillin 50 mg/kg IV, 6-hourly PLUS gentamicin 7.5 mg/kg IV, daily

For children aged 4 months and older, to cover Gram-negative and S. aureus infection, recommended antibiotics are:

- di/fluc/oxa/nafcillin 50 mg/kg (max 2 g) IV, 6-hourly PLUS EITHER cefotaxime 50 mg/kg (max 2 g) IV, 6-hourly OR ceftriaxone 50 mg/kg (max 2 g) IV, daily

Skin or soft tissue source of infection
For severe sepsis resulting from a skin infection (including cellulitis), S. aureus and/or Streptococcus pyogenes are the most likely pathogens. Recommended treatment is:

- di/fluc/oxa/nafcillin 50 mg/kg (max 2 g) IV, 6-hourly

For patients with non-anaphylactic penicillin allergy, we recommend:

- cephalothin 50 mg/kg up (max 2 g) IV, 6-hourly OR cephazolin 50 mg/kg (max 2 g) IV, 8-hourly

For patients with anaphylactic penicillin allergy, we recommend:

- clindamycin 10 mg/kg (max 450 mg) IV or orally, 8-hourly OR vancomycin <12 years: 30 mg/kg (max 1 g) IV, 12-hourly, 12 years or older: 25 mg/kg (max 1 g) IV, 12-hourly

If there is fresh- or saltwater contamination, to cover Vibrios etc. (see Section 14.14, p. 236), we recommend adding:

- cefotaxime 50 mg/kg (max 2 g) IV, 8-hourly OR ciprofloxacin 10 mg/kg (max 400 mg) IV, 12-hourly

15.2 Fluid therapy in severe sepsis
It has been known for some time that vigorous fluid resuscitation improves survival in pediatric septic shock. An observational study compared the outcome of children with septic shock given <20, 20–40, or >40 mL/kg in the first hour after emergency department presentation. Rapid fluid resuscitation >40 mL/kg in the first hour was associated with improved survival, decreased occurrence of persistent hypovolemia, and no increase in the risk of cardiogenic pulmonary edema or adult respiratory distress syndrome.

Question | In children with septic shock, does the use of colloids for fluid resuscitation in comparison to crystalloids reduce mortality or morbidity?

Literature review | We found 53 RCTs, Cochrane review, and a non-Cochrane review comparing colloids with crystalloids in critically ill patients. We found 1 RCT comparing colloid to crystalloid in pediatric septic shock.

Colloids have been used in intensive care for some years, and there is laboratory and animal data to support their use in sepsis. Early systematic reviews comparing colloid and crystalloid in critically ill patients caused alarm, because albumin appeared to be harmful compared with saline. However, the trials in these reviews were small, and more recent systematic reviews, notably the latest Cochrane review, have found that colloids are no worse and no better than crystalloids. Nineteen trials of albumin or plasma protein fraction (7576 patients) reported no effect on mortality (RR 1.02, 95% CI 0.93–1.11). There was no difference between hydroxyethyl starch and crystalloids, between modified gelatin and crystalloid, between dextran and a crystalloid, or between dextran in hypertonic crystalloid and isotonic crystalloid. This Cochrane review has been criticized by intensivists, for the quality of the studies included in the meta-analysis, which nevertheless fulfill the strict Cochrane criteria for inclusion.

Albumin might affect endothelial permeability and redox balance to a different extent to artificial colloids. It is unclear from the above studies, however, whether albumin differs from other colloids, particularly synthetic ones, in outcome.

In a non-Cochrane review of fluid resuscitation for severe sepsis, the authors concluded that albumin
decreased pulmonary edema and respiratory dysfunction compared with crystalloid, while hydroxyethyl starch induced abnormalities of hemostasis.\(^7\)

In the only pediatric RCT, from India, 31 children with septic shock were resuscitated with saline and 29 with gelatin polymer.\(^8\) There was no difference in mortality (29% with saline and 31% with gelatin), and no difference in plasma volume or hemodynamic stability.

The SAFE study\(^9\) was published subsequently to both the Cochrane review\(^6\) and the non-Cochrane review.\(^7\) In the SAFE study, 6997 adult intensive care patients needing fluid resuscitation for any cause were randomized to receive albumin or saline on admission.\(^9\) The mortality of the albumin and saline groups was virtually identical (RR 0.99). A sub-group analysis, however, found that there was a trend for patients with sepsis to be less likely to die within 28 days if they received albumin rather than saline (RR 0.87, 95% CI 0.74–1.02, \(p = 0.09\)). Interestingly, patients with trauma were more likely to die if they received albumin rather than saline.

The colloid versus crystalloid controversy continues, but to date the evidence does not favor either. Considering that colloids are considerably more expensive than are crystalloids, there seems little reason not to use saline. In a setting where resources are scarce, saline is preferable. The critical factor is that timely and vigorous resuscitation with either colloid or crystalloid improves prognosis in septic shock, and that failure to resuscitate adequately with fluids can lead to refractory shock.

We recommend resuscitating children with severe sepsis intravenously using at least 40 mL/kg in the first hour of either crystalloid or colloid.

### 15.3 Vasopressors and inotropes in septic shock

**Question**  
In children with septic shock refractory to intravenous fluid resuscitation, do vasopressors or inotropes compared with standard therapy reduce mortality or morbidity?

**Literature review**  
We found seven observational studies, one RCT,\(^10\) and two non-Cochrane reviews.\(^11,\!12\)

In hypovolemic, cardiogenic, and obstructive forms of shock, the primary defect is a fall in cardiac output leading to tissue hypoperfusion. In septic shock, however, there is a complex interaction between pathological vasodilatation (warm shock), hypovolemia, toxic myocardial depression, and altered distribution of blood flow.\(^11\) Vasopressors such as norepinephrine (noradrenaline) and dopamine vary in their inotropic effect.

We found one RCT which showed that the vasopressor/inotrope milrinone improved cardiac function in children with non-hyperdynamic septic shock, who also received catecholamines.\(^10\) We found two evidence-based reviews of vasopressor and inotropic support in septic shock.\(^11,\!12\) Neither review could find any other RCTs, and their recommendations were mainly reached by consensus. The recommendations, modified from one of the reviews,\(^13\) and the strength of the evidence are given in Box 15.1.

Vasopressors/inotropes are used often if intravenous fluids do not correct shock. A Cochrane review found

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**Box 15.1 Recommendations on vasopressor or inotropic support for children with septic shock.**

1. Monitor arterial blood pressure continuously using an arterial catheter (weak evidence).
2. Give adequate fluid resuscitation (weak evidence).
3. If adequate fluid challenge does not restore arterial pressure and tissue perfusion, give vasopressor or inotrope support (weak evidence, see Box 15.2).
4. Either norepinephrine (noradrenaline) or dopamine is the vasopressor/inotrope of choice to correct hypotension. There is no evidence that using both norepinephrine and dopamine is superior than dopamine alone (weak evidence).
5. Low-dose dopamine should not be used routinely for renal protection (one good RCT\(^13\)).
6. Epinephrine (adrenaline) and phenylephrine should not be first-line vasopressor/inotropes in septic shock (weak evidence).
7. Vasopressin may be considered in patients with refractory shock despite adequate fluids and high-dose vasopressor/inotropes (weak evidence).
8. Dobutamine is the agent of choice for patients with low cardiac output despite adequate fluid resuscitation (weak evidence).
9. Inotropes should not be used to increase cardiac output above physiologic levels (good evidence from two RCTs\(^14,\!15\)).

Modified from Reference 11.
only eight studies comparing vasopressor to placebo, vasopressor to intravenous fluids, or one vasopressor regime with another, using mortality as the outcome. There was insufficient evidence that vasopressin was better than placebo or that a particular vasopressor was superior to other agents in the treatment of shock.

On the other hand, there is one observational study, suggesting that children with septic shock refractory to fluids will respond to inotrope and/or vasopressor therapy. In a study of 50 children with refractory septic shock, the overall 28-day survival was 80%. The children were categorized according to hemodynamic state: those with a low cardiac index responded to an inotrope with or without a vasopressor, those with a high cardiac index and low systemic vascular resistance responded to vasopressor alone, and those with both vascular and cardiac dysfunction responded to combined inotrope and vasopressor therapy.

15.4 Glycemic control in severe sepsis

Hypoglycemia is associated with poor neurologic outcome, and it is obviously important to correct hypoglycemia associated with sepsis. Some septic patients, however, have hyperglycemia, and it is less clear that this should be corrected. There is some evidence that the maintenance of good glycemic control in adults with septic shock improves prognosis, but no good evidence in children.

15.5 Corticosteroids in septic shock

Question | In children with septic shock from any cause, do corticosteroids compared with no steroids or placebo reduce mortality or morbidity?

Literature review | We found no RCTs of corticosteroids in children with septic shock. We found 15 RCTs and a Cochrane review of corticosteroids in adults with septic shock.

A Cochrane review of the use of corticosteroids in adults with septic shock from any cause found 15 RCTs (2023 patients). Corticosteroids did not change 28-day, all-cause mortality (RR 0.92, 95% CI 0.75–1.14) or hospital mortality (RR 0.89, 95% CI 0.71–1.11). Corticosteroids did, however, reduce intensive care unit mortality (RR 0.83, 95% CI 0.70–0.97), and increased the proportion of shock reversal by day 7 (RR 1.22, 95% CI 1.06–1.40) and by day 28 (RR 1.26, 95% CI 1.04–1.52), without increasing the rate of gastrointestinal bleeding, superinfection, or hyperglycemia.

There are no comparable data on corticosteroid use in children. A study of adrenal function in children with septic shock found absolute adrenal insufficiency with catecholamine-resistant shock in 18% and relative adrenal insufficiency in 26% of children. Efficacy studies are needed. Some pediatric intensivists already use intravenous hydrocortisone at a dose of 25 mg/m² 6-hourly (100 mg/m²/day in four divided doses) to treat children with septic shock, but the evidence is weak.

15.6 Intravenous immunoglobulins in severe sepsis

Question | In children with septic shock from any cause, do intravenous immunoglobulins (IVIG) compared with no IVIG reduce mortality or morbidity?

Literature review | We found 27 RCTs of IVIG in septic shock, of which 2 were in children. We found a Cochrane review of IVIG in adults with septic shock.

A Cochrane review of the use of IVIG in septic shock found 27 eligible studies of polyclonal immunoglobulin preparations and specific antibodies, such as monoclonal antibodies (see Section 15.7, p. 247). The overall mortality was reduced in 492 patients who received polyclonal IVIG (RR 0.64, 95% CI 0.51–0.80). A sub-analysis showed that sepsis-related mortality, i.e., deaths caused by sepsis, was significantly reduced in 161 patients who received polyclonal IVIG (RR 0.35, 95% CI 0.18–0.69). For the two high-quality trials on 91 patients of polyclonal IVIG, there was a 70% reduction in mortality, but the confidence intervals were wide (RR 0.30, 95% CI 0.09–0.99). The authors commented that although polyclonal IVIG significantly reduced mortality, all the trials were small and the totality of the evidence is insufficient to support a robust conclusion of benefit.

We recommend considering using IVIG in children with severe and refractory septic shock.
15.7 Monoclonal antibodies in severe sepsis (antiendotoxins and anticytokines)

In the Cochrane review of the use of immunoglobulins, mortality was not reduced among 2826 patients who received monoclonal antibodies, such as antiendotoxins in five good-quality studies (RR 0.97, 95% CI 0.88–1.07), or 4318 patients who received anticytokines (RR 0.93, 95% CI 0.86–1.01). A few studies measured secondary outcomes (deaths from sepsis or length of hospitalization), but no differences in the intervention and control groups were identified in patients receiving antiendotoxin or anticytokine monoclonal antibodies.

15.8 Activated protein C in severe sepsis

In septic shock, there is consumption of coagulation factors including protein C. Although recombinant activated protein C (drotrecogin alfa) reduces mortality from septic shock in adults, it has proven to be of no value in children. A large RCT of activated protein C in children with severe sepsis was halted early by the Data Monitoring Committee because of lack of efficacy (Eli Lilly, 2005).

15.9 Naloxone in severe sepsis

A Cochrane review found six RCTs of naloxone in septic shock. The mean arterial pressure was significantly higher in the naloxone groups than in the placebo groups (weighted mean difference: +9.33 mm Hg; 95% CI 7.07–11.59). Higher blood pressure, however, does not necessarily equate with improved tissue perfusion. The mortality was lower in the naloxone group, but not statistically significantly (OR 0.59, 95% CI 0.21–1.67). The clinical role of naloxone remains unclear.

15.10 Nitric oxide antagonists in severe sepsis

There are theoretical grounds for believing that it might be effective to inhibit nitric oxide synthase. However, the use of a nitric oxide synthase inhibitor in adults and children with septic shock was associated with increased mortality.

15.11 Colony stimulating factors (G-CSF and GM-CSF) in severe sepsis

Recombinant granulocyte colony stimulating factor (G-CSF, filgrastim) was safe but ineffective in reducing mortality in patients with pneumonia and sepsis. We could find no studies of the use of granulocyte macrophage colony stimulating factor (GM-CSF) to treat pediatric septic shock.

15.12 Extracorporeal membrane oxygenation (ECMO) in severe sepsis

Not surprisingly, there are no RCTs of the use of ECMO in septic shock. In one small series, four of nine children with refractory septic shock survived, and the authors concluded that near-fatal septic shock was not a contraindication to ECMO.

15.13 Early goal-directed therapy in severe sepsis

Goal-directed therapy involves adjustments of cardiac preload, after-load, and contractility to balance oxygen delivery with oxygen demand. It has been used successfully in an RCT of adults with septic shock. In this study, mortality was reduced from 46.5% with standard therapy to 30.5% with 6 hours of early goal-directed therapy.

15.14 Sepsis bundles

A “sepsis bundle” is a group of interventions designed to improve the outcome of septic shock. The principle is that patients are assessed to see which of a number of recommended investigations have been performed and which interventions instigated. If it can be demonstrated that compliance with the recommendations in the sepsis bundle is associated with improved outcome, this provides evidence for promotion of the package of interventions as likely to improve outcome. It is not a randomized intervention and is open to selection bias, but it is a reasonable approach given the complexity of intensive care.

The use of sepsis bundles to prevent ventilator-associated pneumonia in a number of adult intensive
care units reduced the mean incidence by 44.5%.27
Sepsis care bundles for systemic sepsis in adults are
used to encourage early monitoring and treatment of
patients. One sepsis bundle28 recorded whether or not
the following targets were achieved at 6 hours:
· serum lactate measured;
· antibiotics given within an hour of taking blood
cultures;
· 0.5 L of fluid given in the first 30 minutes;
· vasopressors for mean arterial pressure <65 mm Hg
despite fluid resuscitation;
· inotropes and/or blood transfusion to target Hb 7–9
g/dL.
At 24 hours, the targets were:
· serum glucose <8.3 mmol/L;
· plateau pressure average <30 cm H2O if ventilated;
· drotrecogin alfa considered for severe sepsis (but note
that this would not be used in children, see above);
· steroids for septic shock;
· APACHE II score;
· predicted mortality.

The rate of compliance with the 6-hour sepsis bundle
was 52%. The mortality was more than twice as high in
the patients for whom the sepsis bundle was not used,
compared with the patients in whom it was used (49% versus 23%, RR 2.12, 95% CI 1.20–3.76) despite similar
age and severity of sepsis. Compliance with the 24-hour
sepsis bundle was achieved in only 30% of eligible can-
didates (21/69). Hospital mortality was higher in the
patients in whom the bundle was not used (50% versus 29%), although the difference did not reach statistical
significance (RR 1.76, 95% CI 0.84–3.64, p = 0.16).
These data suggest that compliance with sepsis bundles,
particularly the early measures, reduces the mortality
from sepsis.28 Sepsis bundles appropriate to children
need to be developed and evaluated.

15.15 Recommendations on the management of severe sepsis in children

The evidence for the recommendations given in Box
15.2 is based on the evidence given above. There have
also been RCTs in adults, described in two overview
papers,30,31 and are difficult to evaluate individually be-
cause of the complex nature of intensive care of the pa-
tient with septic shock. Clearly, there are several inter-
ventions that are urgent: correction of hypoglycemia
(intervention 4 in Box 15.2) is almost as urgent as 1–3.
Antibiotics need to be given as soon as possible, and
any delay could be detrimental.

15.16 Management of specific infections

Meningococcal infection

Clinical diagnosis of meningococcal infection

The differential diagnosis of a child with fever and
petechiae or purpura is discussed in Chapter 6 (see
Section 6.8, p. 62). About 10% of children with fever
and rash have serious bacterial infection and about 7% have meningococcal infection. In a UK case series of 233 children presenting with non-blanching rash, 26 (11%) had meningococcal disease. Children with meningococcal infection were more likely than non-infected children to be assessed as “ill” (not otherwise defined), to be pyrexial (>38.5°C), have purpura, and a capillary refill time <2 seconds.

The management of a well-looked child with petechiae and fever is less clear-cut. The basis for deciding which children need urgent treatment and admission to hospital is discussed in Section 6.7, p. 60.

Not all children with meningococcal infection present with rash. How does the primary care physician or the pediatrician identify children with meningococcal infection without rash? The signs and symptoms of meningococcal infection in infants <1 year and young children aged 1–4 years have been described in detail in a British paper that illustrates the natural history of meningococcal infection.

Parents generally describe a sudden change in the child’s mood or condition. A quarter of all children with meningococcal infection have had symptoms of a cold or upper respiratory tract infection in the 2 weeks prior to being diagnosed with meningococcal infection, but parents still report a sudden change in the child’s behavior or overall condition at what is thought to be the onset of meningococcal infection.

The earliest signs and symptoms of meningococcal infection are non-specific, and may equally well be seen in children with viral infections. Early signs in young children include fever, irritability, vomiting, diarrhea, and anorexia.

After a median of about 4 hours, young children with meningococcal infection may look pale, have cold hands and feet, and those who can talk may complain of limb pains. During the next few hours, they may become drowsy and develop rapid or labored breathing.

If a rash develops, it is on average about 8 hours after the onset of the illness. This rash is characteristically purpuric, meaning it consists of purple dots or bruises due to bleeding into the skin, which do not blanch (go white) on pressure. Less commonly, a less specific, non-blanching rash mimicking a viral rash can occur, and may only develop into the classic purpuric rash over several hours. Interestingly, parents are often advised to compress the rash using a glass tumbler, to see if the skin blanches, and if so, to seek urgent medical advice. A literature search failed to find any evidence that this reliably identifies children with petechiae or with meningococcal infection.

Young children aged 1–4 years in the British study were admitted to hospital a median of 13 hours after the onset of the illness. By this time, most but not all were clearly unwell with fever, tachycardia, tachypnea, and often with rash, shock, and impaired consciousness. The terminal signs of unconsciousness, delirium, or convulsions were seen at about 24 hours.

We use a term “toxicity” or “toxic child” to describe febrile children who are non-specifically unwell. The signs of toxicity are decreased alertness and arousal, altered breathing, blue lips, cold peripheries, weakness, high-pitched cry, and decreased fluid intake and/or urine output (see p. 57). Studies have shown that febrile children who are judged as being toxic are more likely to have serious bacterial infection.

We recommend that all toxic children with fever and rash be sent to hospital urgently (and see p. 250 for recommendations on pre-hospital antibiotics).

We recommend that it is safest to send a non-toxic child with fever and rash to hospital for assessment, especially if the examiner is relatively inexperienced at assessing sick children.

### Prehospital antibiotic treatment of meningococcal infection

The current generally recommended management of a patient in whom *Neisseria meningitidis* infection is suspected on clinical grounds is to give an immediate intramuscular dose of an antibiotic, usually penicillin (see Table 15.1), and arrange urgent transfer to hospital for further treatment. It is also recommended, if possible, that blood cultures or aspirates from skin lesions are collected prior to administration of the antibiotics and sent with the patient to hospital. Although it is intuitive that early antibiotic therapy would reduce mortality, the evidence is limited.

**Table 15.1** Dose of benzylpenicillin prior to hospitalization for suspected meningococcal sepsis.

<table>
<thead>
<tr>
<th>Age of Child</th>
<th>Benzylpenicillin IV or IM</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 year</td>
<td>300 mg (500,000 U)</td>
</tr>
<tr>
<td>1–9 years</td>
<td>600 mg (1,000,000 U)</td>
</tr>
<tr>
<td>≥10 years</td>
<td>1200 mg (2,000,000 U)</td>
</tr>
</tbody>
</table>
Question | For children with meningococcal infection, do preadmission antibiotics compared with no antibiotics reduce mortality?

Literature review | We found 15 observational studies and one non-Cochrane systematic review of the effect of preadmission antibiotics on mortality from meningococcal disease.

We found no RCTs of emergency antibiotic treatment of suspected meningococcal infection, and nor are any likely to be done. Most studies are observational, and these compare patients given preadmission antibiotics with those not given antibiotics. The great problem is confounding by severity: the sickest patients are those who are most likely to be given parenteral antibiotics. A systematic review found that patients given oral antibiotics compared with those not given oral antibiotics (i.e., given no antibiotics or parenteral antibiotics) had a markedly reduced risk of dying from meningococcal infection, with a risk ratio of 0.17 (95% CI 0.07–0.44). Presumably, they were given oral antibiotics because they were not very ill, rather than oral antibiotics being protective. One primary care-based study suggested reduced morbidity and mortality from parenteral antibiotics, while two others found that preadmission parenteral antibiotics were associated with an increase in mortality.

It is plausible that parenteral antibiotics could cause harm, by rapid killing of meningococci causing massive release of endotoxin, leading to shock. In a study of patients with severe meningococcal infection, however, plasma endotoxin levels were high on admission, before antibiotics were given, and did not rise after antibiotics were given.

At present, although the evidence on the benefit of early parenteral antibiotics for suspected meningococcal infection is not strong and may never improve, we think they are more likely to be beneficial than harmful.

We recommend giving parenteral antibiotics to any child seen outside hospital with suspected meningococcal infection (see Table 15.1), and we recommend staying with the child until he or she is admitted to hospital.

In patients with penicillin allergy, or in remote areas where further parenteral therapy may be substantially delayed (>6 hours), we recommend:

- ceftriaxone 50 mg/kg (max 2 g) IV or IM

Emergency Department management of meningococcal infection

A case-control study comparing fatal and non-fatal cases of meningococcal infection in children found three factors independently associated with risk of dying. These were failure to be looked after by a pediatrician, failure of adequate supervision of junior staff, and failure of hospital staff to give adequate inotropes.

Hospital antibiotic treatment of meningococcal infection

For the treatment of acute (or chronic) meningococcal meningitis, we recommend:

- benzylpenicillin 30 mg (50,000 U)/kg (max 1.2 g or 2 million U) IV, 4-hourly for 5 days

For patients with non-anaphylactic penicillin allergy, we recommend:

- ceftriaxone 100 mg/kg (max 4 g) IV, daily for 5 days OR
- cefotaxime 50 mg/kg (max 2 g) IV, 6-hourly for 5 days

For patients with anaphylactic penicillin or cephalosporin allergy, we recommend:

- ciprofloxacin 10 mg/kg (max 400 mg) IV, 12-hourly for 5 days

Corticosteroids in meningococcal infection

Question | In children with septic shock due to meningococcal infection, do corticosteroids compared to no corticosteroids or placebo reduce morbidity or mortality?

Literature review | We found no RCTs of corticosteroids in children with septic shock due to meningococcal infection. We found one non-Cochrane systematic review of corticosteroids for meningococcal infection and 15 RCTs and a Cochrane review of corticosteroids in adults with septic shock from any cause.

We discussed the use of steroids in pediatric septic shock from any infection given in Section 15.5. A non-Cochrane systematic review found no papers that directly studied the use of corticosteroids in children with meningococcal shock. The review concluded...
that high-dose corticosteroids (30 mg/kg of methylprednisolone or equivalent) were detrimental to adults with severe septic shock from any infection, but the use of low-dose corticosteroids (200–300 mg/day of hydrocortisone in adults, equivalent to 5–6 mg/kg/day or 25 mg/m² hydrocortisone IV 6-hourly in children) was promising.

Three papers on adrenal function did not find that children with meningococcal infection developed adrenal failure, but did show what may be an inadequate adrenal response to infection. The authors of the review concluded that the reasonable evidence of benefit from low-dose corticosteroids in adults with severe sepsis plus the evidence of suboptimal adrenal response in children with meningococcal infection supported the use of hydrocortisone replacement therapy in children with meningococcal shock dependent on catecholamines.

We feel that the data are insufficient and would prefer to see RCT data before recommending the use of low-dose corticosteroids in children with meningococcal infection.

Adjunctive therapy with monoclonal antibodies and cytokines in meningococcal infection
There is no evidence to support the use of antibodies against endotoxin in children with meningococcal infection, nor of the use of recombinant human activated protein C, also known as drotrecogin alfa.

Chemoprophylaxis for meningococcal infection
The secondary attack rate in household contacts is increased to 4.2 per 1000 for meningococcal disease (see p. 138). Antibiotic chemoprophylaxis of close contacts of meningococcal cases is recommended, and is also given to the patient (the “index” case) if penicillin is used, because parenteral penicillin does not eradicate carriage. A non-Cochrane systematic review of the effectiveness of prophylactic antibiotics found no high-quality prospective studies, but four retrospective observational studies and one small trial comparing children who did or did not receive chemoprophylaxis. The outcome was secondary cases of meningococcal infection occurring 1–30 days after the index case. Chemoprophylaxis reduced the risk of meningococcal infection for household contacts by an impressive 89%; the risk ratio was 0.11 (95% CI 0.02–0.58), and 218 contacts had to take prophylactic antibiotics to prevent one case of meningococcal infection. In contrast, the data in day care settings were insufficient to judge whether or not chemoprophylaxis is indicated.

A Cochrane review of chemoprophylaxis found no RCTs and no secondary cases, so could not comment on the effectiveness of chemoprophylaxis. It found that ciprofloxacin, minocycline, and rifamp(ic)in were effective at eradicating nasal carriage of meningococcus at 1 week, but only rifampin (RR 0.20, 95% CI 0.14–0.29) and ciprofloxacin (RR 0.03, 95% CI 0.00–0.42) still proved effective at 1–2 weeks. Rifampin continued to be effective compared to placebo for up to 4 weeks after treatment, but resistant isolates were seen following prophylactic treatment. No trials evaluated ceftriaxone against placebo, but ceftriaxone was more effective than rifampin after 1–2 weeks of follow-up (RR 5.93, 95% CI 1.22–28.68).

Because there were no cases of meningococcal disease during follow-up in any of the trials, effectiveness regarding prevention of future disease cannot be directly assessed.

We recommend *N. meningitidis* (meningococcus) prophylaxis for household contacts using:

- rifamp(ic)in: neonate <1 month 5 mg/kg; child 10 mg/kg (max 600 mg); adult 600 mg, orally, 12-hourly for 2 days (preferred option for children) OR
- ciprofloxacin (adult and child ≥12 years) 500 mg orally, child 12.5 mg/kg (max 500 mg) as a single dose OR
- ceftriaxone 250 mg (child 125 mg) IM as a single dose (preferred option during pregnancy)

Rifamp(ic)in is associated with multiple drug interactions, stains contact lenses orange, and is not recommended for persons with severe liver disease. Because they cause cartilage damage in laboratory animals, there are theoretical concerns about quinolones causing skeletal problems in children, although data do not suggest this is a real clinical problem.

Immunization against meningococcal infection
Both conjugate and polysaccharide vaccines are available against meningococci. No conjugate or polysaccharide vaccine is effective against *N. meningitidis* group B. Polysaccharide vaccines have been developed, which incorporate the other serogroups A, C, W-135, and Y. These polysaccharide vaccines are relatively
poorly immunogenic in infancy, and do not produce lasting immunity because the antibody response is generated without T-cell involvement. A conjugate vaccine against serogroup C has been very successful in reducing group C meningococcal disease in the UK\(^6\) and Australia.\(^6\) In the USA, where serogroups B, C, and Y are each responsible for 30% of cases, a conjugate vaccine against A, C, W-135, and Y has been licensed and is recommended for children from 11 to 12 years and for adolescents.\(^7\)

### Staphylococcal toxic shock syndrome

Staphylococcal toxic shock syndrome is a toxin-mediated disease characterized by fever, hypotension, a diffuse sunburnlike erythema, cerebral dysfunction with impaired consciousness, and sometimes convulsions, thrombocytopenia, and multisystem involvement often including evidence of hepatic and renal impairment.\(^7\) The source of the toxin-producing strain of S. aureus may be apparent, such as an infected wound or burn, osteomyelitis, or bacterial tracheitis; may be occult, such as a tampon; or there may be asymptomatic carriage of the organism, with no apparent focus of infection. Aggressive resuscitation and treatment of the source are important aspects of therapy.

There is in vitro evidence that clindamycin reduces toxin production,\(^7\) particularly for streptococcal toxins (see below, streptococcal toxic shock syndrome), but no good evidence that using clindamycin alone or adding it to other antibiotics improves outcome. Clindamycin is recommended if there is a high incidence of community-acquired MRSA and vancomycin should be used if hospital-acquired MRSA is likely, because of prior hospitalization or colonization.

Recommended treatment:

- **clindamycin 15 mg/kg (max 600 mg) IV, 8-hourly** OR
- di/fluc/oxy/nafcillin 50 mg/kg (max 2 g IV), 6-hourly OR
- cephalexin 50 mg/kg (max 2 g) IV, 6-hourly OR
- cephazolin 50 mg/kg (max 2 g) IV, 8-hourly OR
- vancomycin <12 years: 30 mg/kg (max 1 g) IV, 12-hourly, 12 years or older: 25 mg/kg (max 1 g) IV, 12-hourly

A Cochrane review\(^2\) found that polyclonal IVIG reduces mortality in patients with sepsis and septic shock. There is no direct evidence to support the use of IVIG in staphylococcal toxic shock syndrome, but its use could be considered in patients responding poorly to antibiotics and with persistent hypotension. Recommended dose:

- **normal immunoglobulin 1–2 g/kg IV**

### Streptococcal sepsis including streptococcal toxic shock syndrome

Streptococcal toxic shock syndrome has been defined as the isolation of a group A streptococcus (S. pyogenes), hypotension, and two of renal impairment, coagulopathy, liver involvement, adult respiratory distress syndrome, generalized rash, or soft tissue necrosis.\(^7\) It may be less common in children than adults, but when it occurs, it can be fulminant.\(^7\)

There is in vitro evidence that clindamycin reduces toxin production by group A streptococci,\(^7\) but no good evidence from clinical trials that it improves outcome. It should not be used alone because a few strains are resistant.\(^7\) Recommended antibiotics:

- **benzylpenicillin 45 mg/kg (max 1.8 g) IV, 4-hourly PLUS**
- **clindamycin 15 mg/kg (max 600 mg) IV, 8-hourly**

For patients hypersensitive to penicillin (excluding anaphylactic hypersensitivity), substitute for benzylpenicillin:

- **cephalexin 50 mg/kg (max 2 g) IV, 6-hourly OR**
- **cephazolin 50 mg/kg (max 2 g) IV, 8-hourly**

In streptococcal toxic shock syndrome, there is one RCT\(^7\) of 21 patients with streptococcal toxic shock syndrome that found IVIG 1 g/kg on day 1 and 0.5 g/kg on days 2 and 3 was associated with a significant reduction in organ failure and a non-significant reduction in mortality. Although the evidence is not strong, the condition is rare, making large studies difficult. We recommend using IVIG:

- **normal immunoglobulin 1–2 g/kg IV, repeated on days 2 and 3 if hypotension persists**

### References


40 Parikh A, Magonnoche I. What is the use of the glass test? Arch Dis Child 2003;88:1135.
48 Hahne SJM, Charletta A, Purcell B et al. Effectiveness of antibiotics given in admission in reducing mortality from meningococcal disease: systematic review. bmj.com 2006;332:1299.
65 Purcell B, Samuelsson S, Hahne SJM et al. Effectiveness of antibiotics in preventing meningococcal disease after a case: systematic review. bmj.com 2004;328:1339.
69 Committee on Infectious Diseases. Prevention and control of meningococcal disease: recommendations for use


CHAPTER 16
Tropical infections and travel

16.1 Travel

We have not included a chapter specifically covering travel medicine, but have instead dealt with traveler’s diarrhea in Chapter 7, and will cover individual infections in this and other chapters.

For travel advice, the following Web sites are useful:

http://www.cdc.gov/travel
http://www.who.int/topics/travel/en
http://www.travax.nhs.uk

16.2 Brucellosis

Brucellosis is a zoonotic disease, which occurs worldwide in tropical and temperate countries.5 Humans catch it by exposure to domesticated or wild animals through unpasteurized milk or milk products, or contact with carcasses or secretions.

The most common clinical manifestations are fever, arthralgia or arthritis, malaise, weight loss, hepatosplenomegaly, and lymphadenopathy.2–4 The onset is often insidious with ongoing fevers and sweats, although children may present more acutely. Back pain due to lumbar spondylitis is common in adults. Serious complications include endocarditis, meningitis, and osteomyelitis.

The diagnosis is usually made by growing brucella from blood or from bone marrow, CSF, or other tissues. Serology using serum agglutination test (SAT) or enzyme-linked immunosorbent assay (ELISA) is more sensitive for acute brucellosis (42–98%) than for chronic infection (23–64%).4,5 Polymerase chain reaction (PCR) on blood and other tissues, if available, is generally >90% sensitive and >90% specific.6,7

We found six RCTs comparing different antibiotic regimens to treat brucellosis in children. In a large multicenter RCT in Kuwait involving 1100 children, monotherapy with oral oxytetracycline, doxycycline, or rifampin showed comparable results with low relapse rates (9% or less) regardless of duration.8 Trimethoprim-sulfamethoxazole (TMP-SMX) alone had a 30% relapse rate. In combined oral therapy, rifampin plus oxytetracycline, rifampin plus TMP-SMX, and oxytetracycline plus TMP-SMX showed comparable results with low relapse rates ranging from 4 to 8% in patients receiving therapy for 3 or 5 weeks, while no relapses occurred in patients treated for 8 weeks.8

Four of the other studies used doxycycline plus streptomycin as the comparator: two found that doxycycline plus rifampicin was inferior,9,10 while one found that the regimens were equivalent, except perhaps for spondylitis.11 Ceftriaxone was inferior to doxycycline plus streptomycin.12 Finally, an RCT mainly in adults found more treatment failures with doxycycline plus rifampin than with TMP-SMX plus rifampin.13 Regimens using invasive therapy, such as streptomycin and gentamicin (which has been studied in adults),14 have not shown advantages over oral regimens. There have been no studies of quinolones to treat brucellosis in children, and studies in adults are inconclusive.15

To treat brucellosis in children, we recommend:

doxycycline (child >8 years) 2.5 mg/kg (max 100 mg) orally, 12-hourly for 8 weeks OR the combination of
trimethoprim + sulfamethoxazole 6 + 30 mg/kg (max 240 + 1200 mg) orally, 12-hourly for 8 weeks PLUS
rifampicin 15 mg/kg (max 600 mg) orally, daily for 8 weeks

For children with endocarditis, meningitis, or osteomyelitis, it is recommended to give parenteral streptomycin or gentamicin for the first 7–14 days, together with doxycycline (or with TMP-SMX if <8 years old) plus rifampicin.16 The oral antibiotics should be continued, often for several months.16
16.3 Hydatid disease

Hydatid disease in children results from infection with the sheep or cattle tapeworm, *Echinococcus granulosus*. Hydatid disease is common in some parts of the world where the disease is endemic, and extremely rare in others. Dogs and other mammals act as intermediate hosts by swallowing protoscolices of the parasite. They pass embryonated eggs in their feces, which the sheep or cattle swallow. Humans can be infected, and cysts develop in various organs, but humans do not pass on the infection. The commonest places for cysts to grow and cause problems are the liver and the lung. They can also develop elsewhere, such as the central nervous system (CNS), the heart, kidneys, spleen, or thyroid. Commonly, cysts are extremely slow growing and come to notice because they occupy space, e.g., convulsions from cranial hydatid or jaundice from hepatic cyst pressing on bile duct, or because the cyst ruptures.

The diagnosis of hydatid disease may be made histologically (scolices seen in fluid from liver cyst, in sputum, or in CNS cyst), but positive echinococcus serology can support a diagnosis of hydatid disease, while negative serology effectively excludes it. The imidazoles, albendazole and mebendazole, are effective against echinococcus, but may not penetrate large cysts adequately.

Hepatic hydatid cysts

The classic treatment for hepatic cysts is surgical, although there have been recent studies of percutaneous drainage. An RCT found that only 2 of 11 hepatic cysts treated with albendazole reduced in size compared with all 22 treated with percutaneous drainage, with or without albendazole. A systematic review concluded that chemotherapy alone was not as effective as surgery, but there were insufficient studies to distinguish between definitive surgery and percutaneous drainage with or without an imidazoles. This was also the conclusion of a Cochrane review of the “PAIR” technique. PAIR is performed under ultrasound or sometimes computed tomography guidance, and involves percutaneous drainage of the cysts with a fine needle or catheter, aspiration of the contents, instillation of scolicidal substances (e.g., hypertonic saline or absolute alcohol), and reaspiration. An RCT showed that percutaneous drainage plus albendazole was at least as effective as surgery, shortened hospital stay and was associated with fewer complications.

The limited current evidence favors percutaneous aspiration and albendazole. Although it is sometimes recommended to use praziquantel before surgery or if there is cyst spillage, we could find no evidence to support this recommendation. We recommend:

- *albendazole 7.5 mg/kg (max 400 mg) orally, 12-hourly for 1–6 months*

Patients on prolonged albendazole therapy require regular monitoring of liver function tests and white cell count.

Pulmonary hydatid disease

Pulmonary cysts may be picked up as an incidental finding on chest radiograph, or the cyst may rupture into a bronchus, in which case the child may cough up fluid with the appearance of "grape skins," and may develop wheeze, urticaria, or even anaphylaxis. Alternatively, the cyst can rupture into the pleural cavity and cause a pleural effusion. Hydatid lung cysts are more common in boys than girls (1.6–3:1). are often large, unilateral, and right sided, may cause pneumothorax (15% of children in one study) and are associated with hepatic cysts in 10–33% of children but 79% of adults. Treatment of asymptomatic infection is usually not required. We could find no studies comparing medical with surgical management of hydatid lung cysts. In one study, 82 children with lung cysts were treated with albendazole or mebendazole, without surgery. Lung cysts were cured in 34%, improved in 34%, and treatment failed in 32%. Albendazole was more likely than mebendazole to result in improvement. The children who failed had larger cysts (mean 7.3 cm) than those who improved or resolved (5.3 cm).

If it is decided to treat medically, with or without surgery, we recommend:

- *albendazole 7.5 mg/kg (max 400 mg) orally, 12-hourly*

16.4 Malaria

There are four species of the malarial parasite *Plasmodium* that infect humans, of which *Plasmodium falciparum* is the most pathogenic and most resistant to
antimalarials. About 2 billion people are exposed to *P. falciparum* malaria annually, resulting in over 500 million clinical attacks and about a million deaths, predominantly in children less than 5 years living in sub-Saharan Africa. Malaria is also a problem for children returning or immigrating to industrialized countries from tropical regions. Despite the availability of good preventive measures, >10,000 cases of malaria were reported from 1985 to 2001 in US travelers. An estimated 20% of all cases of malaria imported to the USA and Europe occur in children.

Diagnosis of malaria begins with clinical suspicion. In nonimmune children, malaria typically presents with high fever that might be accompanied by sweats, chills, rigors, and headache. Symptoms and signs may be more subtle in partially immune children. Young children are more likely to have signs and symptoms attributable to severe anemia, such as pallor or heart failure. Children may develop cough and tachypnea, mimicking respiratory infection. Other systemic symptoms include nausea, vomiting, diarrhea, abdominal pain, back pain, and arthralgia, while signs include hepatomegaly, splenomegaly, and jaundice. Cerebral malaria can progress rapidly from altered sensorium and confusion to convulsions, coma, hypertension with opisthotonus, decerebrate post-uring, and death. Partially immune children who migrate from endemic areas are often asymptomatic or have isolated splenomegaly.

Malaria should be considered in any patient who has visited a malarious area and presents with fever. A blood sample collected into an EDTA tube should be sent to an appropriate laboratory for examination, including thick and thin films. Thick blood smears help to determine when infection is present, but a single negative blood film or negative antigen test does not exclude the diagnosis of malaria, particularly if antimalarials or antibiotics have been taken recently, because some antibiotics have modest antimalarial activity. Thin blood smears aid in identifying the species of parasite. Antigen and nucleic acid detection tests are available in some specialized laboratories. Rapid antigen tests perform variably, but probably have the same sensitivity as a blood smear. PCR is highly sensitive, but not widely available. In addition, we recommend screening refugees who have recently arrived from an endemic area with a blood film for malarial parasites.

Treatment of acute malaria should include careful supportive care, and intensive care measures should be available for treating children with complicated *P. falciparum* malaria.

### Treatment of malaria

#### Treatment of uncomplicated *Plasmodium falciparum* malaria

The antimalarials of choice will depend on local epidemiology (which *Plasmodium* species are prevalent) and on local resistance patterns. There is a new class of artemisinin (qinghaosu) derivatives, used as artemether, artesunate, and dihydroartemisinin-piperaquine, which have been studied intensely.

The CDC currently advises oral chloroquine for *P. falciparum* infections acquired in the few areas without chloroquine-resistant strains, which include Central America, west of the Panama Canal, Haiti, the Dominican Republic, and most of the Middle East. For pediatric *P. falciparum* infections acquired in areas with chloroquine-resistant strains, they offer three treatment options: quinine sulfate (together with doxycycline, tetracycline, or clindamycin), atovaquone-proguanil, and mefloquine. For children <8 years old, doxycycline and tetracycline are generally not indicated, so quinine is recommended, alone or with clindamycin and atovaquone-proguanil. The third option, mefloquine, is associated with a higher rate of severe neuropsychiatric reactions when used at treatment doses, and is recommended by CDC only when the quinine sulfate combination or atovaquone-proguanil options cannot be used. CDC advises that, in rare instances, doxycycline or tetracycline can be used in combination with quinine in children <8 years old if other treatment options are not available or are not tolerated, and the benefit of adding doxycycline or tetracycline is judged to outweigh the risk. To date, the CDC do not recommend artemisinin derivatives.

### Question

For children with uncomplicated falciparum malaria, do the artemisinin derivatives compared with standard antimalarial regimens reduce mortality or morbidity?

### Literature review

We found 41 RCTs and a Cochrane review of artemisinin derivatives in adults and children with uncomplicated *falciparum* malaria. We found 11 RCTs of artemisinin derivatives in children with
uncomplicated falciparum malaria. We found 16 RCTs and a non-Cochrane meta-analysis of the addition of artemisinin derivatives to standard antimalarial therapy. We found a non-Cochrane systematic review of trials of any antimalarial therapy.

A Cochrane review of artemisinin derivatives for treating uncomplicated falciparum malaria in adults and children found 41 trials (over 5000 patients), but variation in study design and quality made synthesis of the data problematic. Compared with standard antimalarial treatments, artemisinin drugs showed fast parasite clearance and high cure rates at follow-up, provided the duration of treatment with artemisinin drugs was adequate.

We found 11 RCTs in children of combinations of antimalarials, which included one of the artemisinin (qinghaosu) derivatives. The trials were carried out in areas of high resistance to conventional antimalarials in Southeast Asia, Africa, and Bangladesh. Dihydroartemisinin-piperaquine was >99% effective in two studies, had fewer adverse effects than mefloquine+artesunate, and is cheaper. Mefloquine+artesunate was 100% effective in Bangladesh and Lao. Amodiaquine+artesunate and artemether+lumefantrine were >94–100% effective at clearing parasitemia and preventing relapse, except in Nigeria where they were 82.5–87% effective. Regimens using chloroquine with sulfadoxine and pyrimethamine or using amodiaquine alone were only about 60% effective.

A non-Cochrane meta-analysis of the addition of 1 or 3 days of artesunate to standard treatment of P. falciparum malaria found 16 randomized trials (5948 patients), of which only two exclusively studied children. Adding 3 days of artesunate to standard treatment reduced parasitologic failure by 70–80% at days 14 and 28. One day of artesunate was not as effective.

A non-Cochrane systematic review of trials of antimalarials in adults and children found a steady increase in the past 20 years in failure rates reported for chloroquine due to the emergence of chloroquine resistance. Treatment failure rates with sulphadoxine-pyrimethamine were very high in the 1970s and early 1980s, reflecting trials only from Southeast Asia where resistance was emerging, and there has since been a steady increase in treatment failure rates reported from Africa. In contrast, the recrudescence rates for quinine reported over the past 30 years have remained roughly constant. Mefloquine failure rates have increased over the past decade, reflecting the emergence of resistance in Southeast Asia, despite an increase in dosage used (from 15 to 25 mg/kg). Treatment failure rates with artemisinin and its derivatives in combinations (mainly with mefloquine) have remained constantly low, since trials began in the early 1990s.

If a child is admitted with malaria, we recommend seeking advice from an expert and consulting the CDC or WHO Web sites. Artemisinin derivatives appear to be safe and effective, although mefloquine+artesunate is not recommended because of the psychiatric adverse reactions with mefloquine.

For uncomplicated P. falciparum malaria acquired in an area of chloroquine resistance, we recommend:

- **artemether+lumefantrine (20 + 120 mg tablets)**
  - child 5–14 kg: 1 tablet; 15–24 kg: 2 tablets; 25–34 kg: 3 tablets; >34 kg: 4 tablets, orally with fatty food, six doses at 0, 8, 24, 36, 48, and 60 hours OR dihydroartemisinin-piperaquine 2.1 + 16.8 mg/kg orally, once daily for 3 days (tablets are 40 + 320 mg; for children, these can be crushed and given with syrup) OR THE COMBINATION OF quinine sulfate 10 mg/kg (max 600 mg) orally, 8-hourly for 7 days PLUS EITHER clindamycin 10 mg/kg (max 450 mg) orally, 8-hourly for 7 days OR doxycycline child >8 years: 2.5 mg/kg (max 100 mg) orally, 12-hourly for 7 days

In developing countries, cost and availability are important considerations. A comparative trial in the Central African Republic, where artemisinin compounds are not yet available, found that amodiaquine with sulfadoxine-pyrimethamine was 100% effective in uncomplicated malaria and chloroquine with sulfadoxine-pyrimethamine 92.8% effective.

For uncomplicated P. falciparum malaria acquired in an area where there is no chloroquine resistance, we recommend:

- **chloroquine 10 mg base/kg (max 620 mg base = 4 tablets) orally, initially, then 5 mg base/kg (max 310 mg base = 2 tablets) for three doses, one 6 hours later and one each on days 2 and 3**
Treatment of severe malaria (*Plasmodium falciparum*)

Severe malaria is diagnosed if the child has parasitemia and any of the following:
- altered consciousness, hypoglycemia, jaundice, oliguria, or severe anemia;
- parasite count >100,000/mm³ (>2% of red blood cells parasitized);
- vomiting or clinically acidotic.

### Antimalarials for severe malaria (*Plasmodium falciparum*)

**Question**  | For children with severe falciparum malaria including cerebral malaria, do the artemisinin derivatives compared with standard antimalarial regimens reduce mortality or morbidity?

**Literature review**  | We found 16 RCTs and a Cochrane review comparing parenteral or rectal artemisinin derivatives to standard therapy in adults and children with severe malaria, including cerebral malaria. We found 5 RCTs of artemisinin derivatives in children with severe malaria. We found 4 RCTs of artemisinin derivatives in children with cerebral malaria. A Cochrane review found 16 trials (2653 adult and child patients) that compared artemisinin drugs with quinine for severe malaria, including cerebral malaria. Artemisinin drugs were associated with better survival for severe malaria (mortality OR 0.61, 95% CI 0.46–0.82) and also for cerebral malaria. Hypoglycemia was more likely if adults with cerebral malaria were treated with quinine than with artemesinins. We found five studies of artemisinin derivatives in children with severe malaria, which found that they were no better and no worse than conventional treatment with quinine. Three studies comparing rectal artemether with parenteral therapy found that rectal artemether was as effective as parenteral therapy using artemether or quinine. We found four studies of parenteral artemether in cerebral malaria in children. They found that artemesinins were no better and no worse than conventional therapy, and hypoglycemia was equally common. Artether suppositories were as effective as parenteral therapy in two studies. In children with malaria and severe anemia, chloroquine-resistant *P. falciparum* should be assumed to be the infective agent. We recommend establishing intravenous access, starting antimalarial treatment, and seeking expert advice. The recommended dose of artemesunate comes from a large study showing reduced mortality compared to quinine in Southeast Asia.

For treating children with severe malaria, we recommend using artemesinin derivatives if they are available.

We recommend:

- artemesunate 2.4 mg/kg IV, on admission, repeated after 12 and 24 hours, then once daily until oral therapy is possible OR
- artemesunate suppository 10 mg/kg, rectally, once daily until oral therapy possible OR
- quinine dihydrochloride 20 mg/kg loading dose in 5% dextrose IV over 4 hours, then 10 mg/kg IV over 4 hours, 8-hourly (max 1800 mg/day), commencing 4 hours after loading regimen is completed and continuing until the child can tolerate oral treatment.

An initial loading dose of quinine should be given unless the patient has received three or more doses of quinine or quinidine in the previous 48 hours, or mefloquine prophylaxis in the previous 24 hours, or a mefloquine treatment dose within the previous 3 days. Frequent measurements of blood pressure and blood glucose are recommended, because quinine stimulates insulin secretion and can cause hypoglycemia.

When the child can tolerate oral therapy, give a full course of oral antimalarials, as for uncomplicated *P. falciparum* malaria (see p. 259).

If IV quinine is required for longer than 48 hours, seek expert advice, as a dose adjustment may be necessary especially in patients with renal impairment.

### Adjunctive therapy for severe malaria (*Plasmodium falciparum*)

UK guidelines have been published on the management of severe malaria in children, and give important detail on the importance of monitoring for and treating hypoglycemia, the diagnosis and management of shock, the diagnosis and management of seizures and raised intracranial pressure, and the management of disturbances of electrolytes and acid–base balance.
**Fluid therapy for severe malaria** *(Plasmodium falciparum)*

Symptomatic severe malarial anemia has a high fatality rate of 30–40%, and most deaths occur early.64–66 Children with severe malaria with anemia may have been given inadequate fluid resuscitation in the past for fear of heart failure, while children with cerebral malaria are fluid restricted for fear of cerebral edema. This dogma has been challenged recently. Studies in Kenya suggest that children with severe malaria with acidosis have hypovolemia.64,65 A preliminary study of children with severe malaria with anemia examined the safety of pretransfusion management (PTM) by volume expansion. Kenyan children with severe falciparum anemia (hemoglobin <5 g/dL) and respiratory distress were randomly assigned to 20 mL/kg of 4.5% albumin or 0.9% saline or maintenance only (control) while awaiting blood transfusion.65 PTM was apparently safe, since it did not lead to the development of pulmonary edema or other adverse events. The number of children requiring emergency interventions was significantly greater in the control group, 4 of 18 (22%) than the saline group 0 of 20 (p = 0.03).65

A subsequent RCT compared 4.5% albumin with normal saline for children with severe malaria and metabolic acidosis (base deficit >8 mmol/L).66 There was no significant difference in the resolution of acidosis between the groups, but the mortality rate was significantly lower among patients who received albumin (3.6%, 2 of 56 patients) than among those who received saline (18%, 11 of 61; RR 5.5, 95% CI 1.2–24.8, p = 0.013). Larger studies are under way, but these data are convincing enough to recommend albumin in preference to normal saline for resuscitation of children with severe malaria and acidosis.

A recommendation62 to transfuse all children with severe malaria and a hemoglobin <10 g/dL is somewhat controversial. A Cochrane review67 found only two RCTs in 230 children. The reviewers could not reach a conclusion for or against transfusion, because the transfusion group had a non-significant trend toward fewer deaths (RR 0.41, 95% CI 0.06–2.70) but also a trend toward more severe adverse events (RR 8.60, 95% CI 1.11–66.43).67 The lower the hemoglobin the greater the need for transfusion, but albumin can safely be used while awaiting blood.65,66

**Treatment of malaria due to Plasmodium vivax, Plasmodium malariae, and Plasmodium ovale**

Although there is widespread chloroquine resistance of *P. falciparum*, non-falciparum malaria parasites are generally sensitive to chloroquine in most parts of the world. This is true even for places like Thailand, where all *P. falciparum* are chloroquine resistant.68 However, in 1989, chloroquine-resistant *P. vivax* was described in Indonesian Papua New Guinea,69 and it has been described since in Indonesia, Myanmar, India, and Guyana in South America.70 In Indonesia, mefloquine has been shown to be an effective alternative to chloroquine for treating *P. vivax* infection.71 To treat non-falciparum malaria, unless contracted in an area of chloroquine-resistant *P. vivax*, we recommend:

- **chloroquine 10 mg base/kg (max 620 mg base = 4 tablets) orally, initially, then 5 mg base/kg (max 310 mg base = 2 tablets) for three doses, one 6 hours later and one each on days 2 and 3**

To treat non-falciparum malaria when chloroquine-resistant *P. vivax* is prevalent, we recommend:

- **mefloquine 15 mg/kg (max 750 mg) orally, initially, then 10 mg/kg (max 500 mg) 8–12 hours later**

Artemether derivatives clear parasitemia rapidly and may be an alternative, but data are scanty.72 We advise seeking expert advice for children with vivax malaria, who fail treatment with chloroquine.

Chloroquine and mefloquine act on the blood stages of the parasite, but do not eliminate the liver forms and relapse is fairly common. A 14-day course of primaquine is recommended by the WHO to reduce treatment failure or relapse.73 In RCTs in India and Pakistan, 14 days of primaquine is 50–70% effective in preventing relapses.74,75 Five days of primaquine is ineffective.76 Primaquine-tolerant strains of *P. vivax* have been reported from Thailand, where up to 18% of people being treated with standard primaquine regimens relapse.77
To eliminate liver forms of *P. vivax* and *P. ovale* infections, we recommend adding to chloroquine or following within a few days with:

**primaquine 0.3 mg/kg (max 15 mg) orally, daily with food for 14 days**

[NB: Primaquine is not recommended for children <4 years old.\(^{73}\) Patients should be tested for glucose-6-phosphate dehydrogenase (G6PD) deficiency before using primaquine, which should not be used in G6PD-deficient children, in whom it can cause severe hemolysis.\(^{73}\)]

If the patient relapses after the primaquine treatment, it may be necessary, after treating the infection with chloroquine or mefloquine, to double the dose of primaquine or treat for longer. We recommend seeking expert advice.

If the patient is unable to tolerate oral therapy, which is best taken with food, we recommend treating as severe malaria as above and consulting an experienced specialist.

### Prevention of malaria

**Insecticide-treated bed nets**

**Question** | For children in malarious areas, do insecticide-treated bed nets (ITNs) compared with no nets or untreated nets reduce the frequency of episodes of malaria and reduce mortality?

**Literature review** | We found 22 trials and a Cochrane review.\(^{78}\)

Insecticide-treated bed nets are highly effective in reducing childhood morbidity and mortality from malaria. A Cochrane review\(^ {78}\) found 14 cluster randomized trials (where clusters or groups of children, such as villages, were randomized to ITNs or no ITNs), and eight RCTs where individual children were randomized. ITNs reduced deaths in children by 17–23% and episodes of malaria by about 50%. ITNs can save 5–6 lives each year for every 1000 children protected with ITNs.\(^ {78}\)

**Vector avoidance**

Other vector-avoidance measures apart from ITNs are recommended,\(^ {78}\) and although dictated by common sense, have not been studied in trials. These are:

- using topical insect repellent;
- wearing long trousers and long-sleeved shirts in the evening and the early morning;
- not going outdoors between the evening and the early morning;
- avoiding perfumes and aftershave.

### Chemoprophylaxis

**Question** | For children living in or visiting malarious areas, does regular chemoprophylaxis with antimalarials compared with no prophylaxis or placebo reduce the frequency of attacks of malaria?

**Literature review** | We found four RCTs of regular prophylaxis and a Cochrane meta-analysis\(^ {79}\) of prophylaxis and intermittent treatment.

Because of the relatively low rate of malaria in visitors and for ethical reasons, it would be difficult to study the efficacy of chemoprophylaxis for visitors to malarious areas in an RCT. It is possible, however, to study chemoprophylaxis in young children who live in those areas. Children living in areas where malaria is endemic acquire natural immunity to malaria by 7–10 years of age.\(^ {80,81}\) Before this age, children living in malarious areas have inadequate immunity to malaria, which is why most of the 1 million malaria deaths that occur each year in endemic areas of sub-Saharan Africa occur in this age group.\(^ {27}\)

A Cochrane review of antimalarials in children up to 6 years old living in malarious areas found 18 eligible RCTs, all in Africa.\(^ {79}\) Eight studies examined episodes of clinical malaria as an outcome: four RCTs of regular chemoprophylaxis and four RCTs of intermittent treatment for episodes of presumed malaria (sometimes called “febrifuge”). Chemoprophylaxis reduced the number of episodes by 43% (RR 0.57, 95% CI 0.33–1.00, 2806 participants). Intermittent treatment had a similar effect, and when the eight trials were combined, antimalarial drugs were statistically significantly better than placebo at preventing clinical malaria (RR 0.52, 95% CI 0.35–0.77). Severe anemia was also reduced by about half. An analysis of nine trials (7929 participants) did not detect a significant difference in mortality (RR 0.82, 95% CI 0.65–1.04) but the confidence intervals do not exclude a potentially important difference. None of the trials reported serious adverse events.\(^ {79}\) It appears that there is good evidence to support chemoprophylaxis
or intermittent treatment for children living in malarious areas, and this adds weight to recommendations for giving chemoprophylaxis to children visiting malarious areas.

Web sites for advice on antimalarial prophylaxis for children

The development of widespread multidrug-resistant strains of *P. falciparum* throughout the world, particularly Southeast Asia, complicates recommendations for prophylaxis. Useful information regarding the malaria risk and the drug susceptibility profile for specific geographic locations is available from the CDC, and WHO Web sites.


Travel medicine clinics, travel advisory services, and other experts can also provide appropriate information.

Recommendations on antimalarial prophylaxis for children

No drug regimen is completely safe and effective. The decision to use chemoprophylaxis must, therefore, weigh the risk of disease against the efficacy and toxicity of the drugs. The risk of acquiring malaria depends on factors such as the country visited, whether the visit is to urban or rural areas, the time of year, the duration of visit, and the type of activities undertaken. In some places, notably many major cities and tourist resorts in malaria-endemic countries, the risk of malaria is low and the risk of prophylaxis outweighs the risk of malaria. In this case, travelers should be advised against prophylaxis.

There are problems with chemoprophylaxis for children of availability of appropriate drugs and of adherence. Doxycycline can cause rash and esophagi-
serious adverse events, including neuropsychiatric ones with mefloquine.

For prophylaxis in areas with chloroquine-resistant malaria (including Africa, China, the Indian subcontinent, the Pacific Islands, Southeast Asia, and South America), we recommend:

atovaquone + proguanil:
11–20 kg: 1 tablet of 62.5 + 25 mg pediatric formulation
21–30 kg: 2 tablets of 62.5 + 25 mg pediatric formulation
31–40 kg: 3 tablets of 62.5 + 25 mg pediatric formulation
>40 kg: 1 tablet of 250 + 100 mg adult formulation

orally, with fatty food, daily (starting 1–2 days before entering, and continuing until 7 days after leaving malarious area) OR
doxycycline: child >8 years: 2.5 mg/kg (max 100 mg) orally, daily (starting 2 days before entering, and continuing until 4 weeks after leaving malarious area) OR
mefloquine 5–9 kg: 31.25 mg (1/8 of 250 mg tablet); 10–19 kg: 62.5 mg (1/4 tablet); 20–29 kg: 125 mg (1/2 tablet); 30–44 kg: 187.5 mg (3/4 tablet) orally, weekly (starting 2–3 weeks before entering, and continuing until 4 weeks after leaving malarious area)

Alternatively, for limited areas of Africa, some authorities recommend:

chloroquine 5 mg base/kg (max 310 mg base or 2 tablets) orally, weekly (starting 1 week before and continuing until 4 weeks after leaving malarious area) PLUS
proguanil <2 years: 50 mg; 2–6 years: 100 mg; 7–10 years: 150 mg; >10 years: 200 mg, orally, daily (starting 1 week before entering, and continuing until 4 weeks after leaving malarious area)

Areas with mefloquine-resistant malaria
For prophylaxis in areas with mefloquine-resistant malaria (including parts of Southeast Asia), we recommend atovaquone + proguanil or doxycycline (see below).

Emergency treatment of malaria (febrifuge)
Some authorities recommend that travelers who elect to not use chemoprophylaxis, or who elect to use chloroquine for chemoprophylaxis in areas with chloroquine-resistant malaria, can be given a “standby” course of artether + lumefantrine or atovaquone + proguanil, or a single dose of mefloquine for self-treatment of fever if medical care is not likely to be available within 24 hours (see pp. 259–61). However, travelers should be warned that uncertain diagnosis is a potential problem. Treatment courses of antimalarial drugs can often be bought without a prescription in tropical countries, but counterfeit products are common.

16.5 Melioidosis
Melioidosis is caused by the soil saprophyte, *Burkholderia pseudomallei*. It occurs mainly in tropical parts of the Asia-Pacific region and in northern Australia, but also in Brazil, and cases have been reported from Puerto Rico and the West Indies. Melioidosis may present in returned travelers, sometimes months or years after exposure.

Adult diabetics and alcoholics are at particular risk of developing severe illness, but children can be affected. Children either develop a septicemic illness, with or without pneumonia and splenic abscesses, or they have localized disease with ulcers or abscesses in the skin, soft tissues, and lymph nodes. Parotitis and pharyngocervical diseases are seen in Thailand, and encephalomyelitis in Australia.

There is an association with chronic granulomatous disease. Neonatal cases have occurred and have been ascribed to breast milk transfer.

Selective culture media, serology, and a PCR test assist diagnosis.

We found 16 RCTs and a Cochrane review on treatment of melioidosis. Only one study included children. All studies, including the one involving children, showed that cefazidime halved mortality in acute severe melioidosis, while the addition of other drugs did not help. For initial intensive therapy, we recommend:

cefazidime 50 mg/kg (max 2 g) IV, 6-hourly for at least 14 days
Granulocyte colony-stimulating factor therapy has been used in northern Australia, and in an historical observational study, its introduction was associated with a fall in mortality from 95 to 10%.

After the initial intensive therapy, eradication is recommended. Two RCTs have shown that triple therapy with trimethoprim, sulfamethoxazole, and doxycycline is better tolerated than quadruple therapy using the three drugs plus chloramphenicol and more effective than ciprofloxacin plus azithromycin. We recommend:

trimethoprim + sulfamethoxazole 8 + 40 mg/kg (max 320 + 1600 mg) orally, 12-hourly for at least a further 3 months PLUS (if >8 years) doxycycline 2.5 mg/kg (max 100 mg) orally, 12-hourly for at least a further 3 months

16.6 Q fever

Q fever is caused by the intracellular rickettsial organism, *Coxiella burnetii*. It is a zoonosis, acquired most often from sheep, goats, and cows, although mammals, including cats, dogs, rodents, and marsupials, and birds can also transmit infection to humans. High numbers of *C. burnetii* are present in the placenta of infected parturient animals, and are shed in the environment following labor or abortion. Humans acquire the infection mainly by inhaling contaminated aerosolized particles or ingesting unpasteurized dairy products, including milk and cheese. Outbreaks have been reported following exposure to birth products of cats, dogs, and rabbits.

Most infections are asymptomatic. Pediatric cases are rarely reported: a review found only 46 published cases in children. Acute self-limited febrile illness and pneumonia are the most common manifestations of acute Q fever in children, but meningitis, hepatitis, and hemolytic-uremic syndrome have also been reported. Chronic disease, manifesting as endocarditis and osteomyelitis, is very rarely reported in children.

Culture is hazardous to laboratory staff and is not usually attempted. Diagnosis is by serology or PCR. An immunofluorescent antibody (IFA) test has been shown to perform better than an ELISA or CFT. The use of both PCR and IFA improves diagnostic accuracy.

We found only one RCT of treatment of Q fever pneumonia, in which doxycycline resulted in more rapid resolution of fever than did erythromycin. Chloramphenicol had been used, but we could find no trials. In observational studies, adult patients treated with clarithromycin and moxifloxacin defervesced as quickly as those given doxycycline, and may be alternatives. We recommend:

doxycline >8 years: 2.5 mg/kg (max 100 mg) orally, 12-hourly for 14 days OR
clarithromycin 12.5 mg/kg (max 500 mg) orally 12-hourly for 14 days OR
moxifloxacin 10 mg/kg (max 400 mg) orally or IV, daily for 14 days

Chronic disease, particularly endocarditis, is rare, and the organism is extremely difficult to eradicate, requiring prolonged therapy usually with at least two drugs.

16.7 Schistosomiasis (bilharziasis)

Schistosomiasis (bilharziasis) is a disease caused by trematode worms of the genus *Schistosoma*. Humans are the principal host, and certain fresh-water snails are the intermediate hosts. Eggs excreted into fresh water in the stool (*S. mansoni*, *S. japonicum*) or urine (*S. haematobium*) hatch into motile miracidia, which infect snails. The organism develops in the snail into infecting larvae or cercariae, which can penetrate human skin.

About 200 million people are infected worldwide, almost all in tropical countries. *S. mansoni* occurs in tropical Africa, the Caribbean, Brazil, Venezuela, Surinam, and the Arabian peninsula. *S. haematobium* occurs in Africa and the eastern Mediterranean. *S. japonicum* occurs in China, Indonesia, and the Philippines.

Acute schistosomiasis is mostly seen in travelers after primary infection. *S. mansoni* and *S. japonicum* can cause Katayama fever, usually 4–8 weeks after exposure, with fever, malaise, nausea, abdominal pain, diarrhea (which can be bloody and mucoid in heavy infection), cough, rash, lymphadenopathy, and sometimes hepatomegaly. Eosinophilia is common. Swimmer’s itch is not caused by human strains, but
by non-pathogenic avian and mammalian species of Schistosoma.

Chronic schistosomiasis affects mainly individuals with long-standing infections in poor, rural areas. Immunopathological reactions against schistosome eggs trapped in the tissues lead to inflammatory and obstructive disease of the urinary system (S. haematobium) or intestinal disease, hepatosplenic inflammation, and liver fibrosis (S. mansoni and S. japonicum). Untreated, these can lead to hematuria, to calcification of the bladder and lower ureters, resulting in hydroureret and hydronephrosis, and to bladder cancer (S. haematobium) or can lead to cirrhosis of the liver (S. mansoni and S. japonicum).

The microscopic examination of stool or urine for ova is the gold standard for the diagnosis of schistosomiasis. Antibody-based assays are sensitive and are important for diagnosis in travelers, migrants, and other occasionally exposed people. They cannot distinguish past exposure from active infection; and can cross-react with other helminths, so are not useful in field conditions.

Because of the risk of chronic schistosomiasis and the ease of treatment, we recommend screening migrants from endemic areas, using stool and urine microscopy or serology, and treating those who are infected.

A Cochrane review of 13 trials found that both praziquantel, an acylated quinoline-pyrazine active against all schistosome species, and oxamnique were active against S. mansoni. However, oxamnique is not active against other Schistosoma species and is only used in Brazil. Praziquantel is less toxic than oxamnique, cheap, and effective in children, and is the recommended treatment of choice. Adverse effects are usually mild, although occasionally a child who is heavily infested will develop colic, vomiting, diarrhea (sometimes bloody), urticaria, and edema within hours of taking praziquantel, probably provoked by massive worm shifts and antigen release.

Katayama fever is often treated with corticosteroids to suppress the hypersensitivity reaction together with praziquantel to eliminate the already matured worms, although there are no RCTs.

Praziquantel should be administered with great caution in neurocysticercosis because of the danger of convulsions. Corticosteroids and anticonvulsants are possible adjuvant therapies to reduce the risk. The management of neurocysticercosis is complex, and we recommend expert advice.

For infection with S. haematobium and S. mansoni, we recommend:

**praziquantel 20 mg/kg orally, after food, and a second dose 4 hours later**

The child’s urine and/or stools should be checked 6 weeks later to make sure the treatment has been successful, and the course repeated if ova persist.

Infections with S. japonicum and S. mekongi are somewhat more resistant. We recommend:

**praziquantel 20 mg/kg orally, for three doses after food, 4 hours apart**

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**References**

43 van den Broek IV, Maung UA, Peters A et al. Efficacy of chloroquine + sulfadoxine—pyrimethamine, mefloquine + arsunate and artemether + lumefantrine combination therapies to treat *Plasmodium falciparum* malaria in the


78 Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. The Cochrane Database of Systematic Reviews 2004;(2):Art No CD000365.


17.1 Acute urinary tract infection

Acute urinary tract infection (UTI) is common in children. Most UTIs in children result from ascending infections. Neonates with UTI are often septicemic, but that does not necessarily mean, as often stated, that neonatal UTI occurs due to hematogenous spread. It could be that UTI is due to ascending infection, but UTI is more likely to be complicated by septicemia in neonates. Indeed, neonatal UTI is often associated with urinary tract abnormality, implying local infection followed by bloodstream spread. Boys are more susceptible to UTI than girls before the age of 3 months, because of a higher incidence of anatomic abnormalities. Thereafter, the incidence is substantially higher in girls. Estimates of the true incidence of UTI depend on rates of diagnosis and investigation. At least 8% of girls and 2% of boys will have a UTI in childhood.

Hospitalization is required in about 40% of cases, particularly in infancy. Transient damage to the kidneys occurs in about 40% of affected children, and about 5% suffer permanent damage, sometimes even following a single infection. Symptoms are systemic and non-specific rather than localized in early childhood, consisting of fever, lethargy, anorexia, vomiting, and sometimes rigors.

Children who have had one infection are at risk of further infections: 30–40% of children who have had an initial UTI will have another UTI, and up to 30% will have recurrent UTIs. The risk factors for recurrent infection are vesicoureteric reflux (VUR) leading to dilatation, bladder instability, and previous infections. Recurrence of UTI is more common in girls than boys. The major significance of UTI is the risk of renal damage, and this risk increases as the number of recurrences increases.

The question of circumcision (see p. 277) and prophylactic antibiotics (see p. 278) to prevent UTI and reduce renal damage are considered below.

Definition of acute UTI

Urine is normally sterile. Girls may have asymptomatic bacteriuria, and an RCT showed that antibiotic treatment of schoolgirls with asymptomatic bacteriuria was not only of no benefit but caused more symptoms than did placebo. In contrast, expert opinion is that children with symptomatic UTI benefit from antibiotics, although it would not be ethical to perform placebo-controlled trials to prove this.

Traditionally, the definition of UTI has been a pure growth of 100,000 (10^5) colony-forming units (CFU) per milliliter from a voided specimen. This figure comes from Kass’ studies, comparing voided specimens from women who were about to be catheterized with catheter specimens, and has never been verified in children. Using this figure as the definition of UTI, a comparative study arrived at the figures given in Table 17.1 to reach a definition of UTI when urine is collected by different methods.

UTI is caused by Escherichia coli in over 80% of cases. Other organisms include Proteus (which is more common in boys and in children with renal stones), Klebsiella, Enterococcus, and coagulase-negative staphylococci. The doubling time of E. coli in urine is less than an hour, so urine that sits on the bench for any length of time may give a false-positive culture.

Table 17.1 Bacteriologic diagnostic criteria for acute UTI in children.

<table>
<thead>
<tr>
<th>Method of Urine Collection</th>
<th>Minimum Level of Bacteriuria for Diagnosis of UTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clean catch in girls</td>
<td>100,000 (10^5) CFU/mL (or 10^6/L)</td>
</tr>
<tr>
<td>Clean catch in boys</td>
<td>10,000 (10^4) CFU/mL (or 10^5/L)</td>
</tr>
<tr>
<td>Catheter</td>
<td>10,000 (10^4) CFU/mL (or 10^5/L)</td>
</tr>
<tr>
<td>Suprapubic aspiration</td>
<td>Gram-negative bacilli: any colonies</td>
</tr>
<tr>
<td></td>
<td>Gram-positive cocci: 5000 CFU/mL (or 5 x 10^5/L)</td>
</tr>
</tbody>
</table>

CFU/mL = colony-forming units per mL (sometimes expressed as organisms/mL).
Method of urine collection

Urine can be collected by clean catch voiding, bag, pad, suprapubic aspiration (SPA), or catheterization. In an acute situation, when empiric antibiotics will be started regardless of urinalysis, it is important to get the specimen using a method which is both sensitive and specific, so as to be able to rely on the culture result as the basis for future decisions about investigation and ongoing management. On the other hand, if there is less urgency because treatment will not be started immediately, a less invasive test may be preferred, even it is much less specific.

Question | For children with suspected UTI, is one method of urine collection compared to others more sensitive, more specific, or more acceptable?

Literature review | We found seven studies^{15–21} and a non-Cochrane systematic review^{22} directly comparing different urine collection techniques.

Bag and pad specimens are contaminated (defined as $10^5–10^6$ CFU/mL) in 16–29% of specimens.^{15,16} Although this is sometimes said to be too inaccurate, these techniques are simple and minimally invasive. If the culture is negative, this excludes UTI and avoids more invasive tests. If the bag or pad culture grows an organism, the test can be repeated using a more specific collection method. On the other hand, the routine use of bag specimens to test urine from febrile children attending emergency departments tends to lead to overdiagnosis and overtreatment.^{17} In one study, banning bag specimens reduced the number of urine specimens sent to the laboratory and reduced the number of children treated unnecessarily, without any reduction in the number of true UTIs diagnosed.^{17}

Clean voided or clean catch urines often take time and patience to collect, and are contaminated in 2–15% of cases.^{15,16}

Specimens collected by SPA or urethral catheter are very rarely contaminated, although an SPA can inadvertently puncture the bowel and a catheter specimen can be contaminated with perineal bowel organisms. A systematic review of rapid tests to diagnose UTI also looked at the accuracy of sampling techniques in terms of contamination.^{22} Thirteen studies compared the results of culture from urine obtained by different sampling methods. When both clean voided urine samples and SPA urine samples were cultured (five studies), the agreement between the two sampling methods was good. Overall, there were insufficient data to draw any conclusions regarding the appropriateness of using urine samples obtained from bags (four studies) or pads/nappies (four studies).^{22}

Invasive sampling procedures are not always successful. In one study, SPA yielded urine in only 62% of attempts, improving to 93% when ultrasound was used to locate the bladder.^{18} Similarly, initial catheterization was successful in only 72% of children, but 93% if ultrasound was used first to make sure there was urine in the bladder.^{19} We found two RCTs comparing SPA and catheterization.^{20,21} In one study, at least 2 mL of urine was obtained from all 50 children randomized to catheterization, but only 46% of 50 who underwent SPA. After failed SPA, urethral catheterization was 100% successful.^{20} A second small study found that an adequate urine sample was obtained from 66% with SPA and 83% with catheter, but that pain scores were significantly higher with SPA.^{21}

Catheter urine samples are more likely to obtain urine and less painful than SPA, and are recommended as the method of choice when it is urgent to get a urine specimen.

Appearance of urine

Cloudy urine is often interpreted as meaning a definite UTI. In practice, about half of all symptomatic children with cloudy urine have a UTI.^{23–25} If a symptomatic child has cloudy urine, the urine should be sent for culture, because it is important to know whether or not there is a true infection, which has major implications for investigation and management.

Some have claimed that a crystal clear appearance on visual inspection of urine excludes UTI.^{23} This has been refuted by studies which found that 3–4% of crystal clear urine samples grew $10^5$ organisms/mL or greater, and the patient was diagnosed as having a UTI.^{24,25}

Urinalysis to detect UTI

It would be useful if urinalysis could predict whether a child was or was not likely to have a UTI, in terms of whether or not to send urine for culture and whether or not to start empiric therapy. A dipstick test would be the simplest rapid test, giving an answer in seconds. Microscopy for bacteria and/or white cells can
be performed in the office but requires training and a bit more time.

**Question** | In febrile young children, does urinalysis reliably detect UTI?

**Literature review** | We found two non-Cochrane meta-analyses of urinalysis screening tests\(^{26,27}\) and two non-Cochrane systematic reviews.\(^{22,28}\)

A non-Cochrane meta-analysis of 26 studies\(^{26}\) found that any organisms seen on gram stain had 93% sensitivity and 95% specificity for detecting UTI, and a dipstick test positive for both nitrite and leukocyte esterase performed almost as well, with a sensitivity of 88% and a specificity of 93%. These performed better than pyuria (defined as > 10 white cells/mm\(^3\)), which was only 77% sensitive.

A subsequent non-Cochrane meta-analysis of 48 studies used a different technique, so-called receiver operator curves, to analyze sensitivity and specificity together, and concluded that pyuria (10 or more white cells per high-power field) and bacteriuria (any bacteria on gram stain) performed best.\(^{27}\)

A non-Cochrane systematic review to determine the diagnostic accuracy of rapid tests for detecting UTI in children <5 years old found 70 studies, of which 39 evaluated dipstick tests.\(^{22}\) The review concluded that either a dipstick positive for both nitrite and leukocyte esterase or microscopy positive for both pyuria and bacteriuria made UTI extremely likely. Similarly, they concluded that a dipstick negative for both nitrite and leukocyte esterase or microscopy negative for both pyuria and bacteriuria effectively excluded UTI.\(^{22}\)

If rapid tests can identify children with UTI with a high degree of probability, they can be used as a basis for choosing children who should start empiric therapy. The best specificity (98%) in the two meta-analyses was for nitrite.\(^{26,27}\) If specificity is high, false positives are rare, so a positive nitrite could be used as a basis to start empiric therapy.\(^{28}\) It could be argued that if the child gets better with empiric antibiotics and the diagnosis of UTI does not mandate any investigations, there is no need to send urine for culture. We still recommend sending urine for culture, however, because of the need to know the antibiotic sensitivity of the bacteria and because we feel it is important to confirm UTI.

If rapid tests can identify children who are very unlikely to have UTI, the clinical options are to withhold antibiotics but send urine for culture or to decide that UTI has been effectively excluded and it is not necessary to send urine for culture. If both nitrite and leukocyte esterase are negative on dipstick, UTI is extremely unlikely. A clinical decision should be made whether to send urine for culture and withhold antibiotics, or to discard the urine and consider other diagnoses.\(^{28}\)

**Febrile children and urine culture**

One study of over 4000 children <2 years attending an emergency department with fever compared culture with microscopy of catheter urines. There were 212 children with positive urine cultures. They found that the presence of pyuria had 95% sensitivity for UTI. If urine cultures had been performed only on specimens from children who had pyuria or who were managed presumptively with antibiotics, cultures of 2600 (61%) specimens would have been avoided, but 22 of 212 patients with positive urine cultures would not have been identified.\(^{29}\) It is arguable whether the cost saved by not sending 2600 specimens justifies missing 22 UTIs.

Sending urine cultures routinely on febrile children with clinical evidence of respiratory infection or another focus of infection and who are not really suspected of having UTI is illogical. It will yield many false-positive urine cultures if a bag specimen is used, and is unnecessarily traumatic if invasive techniques are used.

**Empiric antibiotic treatment for UTI**

**Question** | In children with UTI, is oral antibiotic therapy compared to short-term intravenous followed by oral antibiotics effective in terms of immediate and long-term outcomes?

**Literature review** | We found 18 RCTs and a Cochrane review.\(^{30}\)

The Cochrane review\(^{30}\) was called “Antibiotics for Acute Pyelonephritis in Children.” According to the Cochrane authors, acute pyelonephritis is the most severe form of UTI in children and is different from acute cystitis. They define acute cystitis and pyelonephritis as follows:

- **Acute cystitis:** This infection is limited to the urethra and bladder, seen most commonly in girls over 2 years of age, and presenting with localizing symptoms of dysuria (pain when passing urine), frequency, urgency, cloudy urine, and lower abdominal discomfort. Pyuria
(white cells in the urine) and hematuria (blood in the urine) may also be found.\(^{30}\)

- **Acute pyelonephritis:** This is infection of the kidney, associated with systemic features such as high fever, malaise, vomiting, abdominal and loin pain, and tenderness, poor feeding, and irritability in infants. Together with urine culture, diagnosis may be assisted by imaging using \(^{99m}\)Tc-labeled dimercaptosuccinic acid (DMSA) renal scan and markers of inflammation in the blood, such as erythrocyte sedimentation rate and C-reactive protein.\(^{30}\)

  The Cochrane review included studies of children with UTI, who had one or more systemic symptoms.\(^{30}\) The reviewers found 18 eligible trials (2612 children). No significant differences were found in persistent renal damage at 6 months (but based on only one trial, of 306 children: RR 1.45, 95% CI 0.69–3.03), or in duration of fever between oral cefixime therapy (14 days) and IV therapy (3 days) followed by oral therapy (10 days). Similarly, no significant differences in persistent renal damage (RR 0.99, 95% CI 0.72–1.37) were found between IV therapy (3–4 days) followed by oral therapy and IV therapy for 7–14 days. However, only two studies included neonates, a third of the studies did not include babies <3 months old, and it was not possible to look at outcome by age to see if younger children might benefit more from IV therapy. It is known that the incidence of septicemia with UTI is 4–10% overall, and is highest in younger children.\(^{31–34}\)

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**We recommend treating children 3 months and older with acute pyelonephritis with oral cefixime or with short courses (2–4 days) of IV therapy followed by oral therapy.**

**We recommend commencing neonates and infants <3 months old on IV therapy, because the risk of septicemia is high\(^{31–34}\) and it has not been shown that commencing with oral antibiotics is as effective as IV treatment at this age.**

**Question** | In children with UTI, is short-course antibiotic treatment compared with 5 days or more of antibiotics effective in terms of immediate and long-term outcomes?

**Literature review** | We found a non-Cochrane meta-analysis comparing short-duration with long-duration antibiotics for acute cystitis in children,\(^{35}\) and a non-Cochrane meta-analysis\(^{36}\) and a Cochrane review\(^{37}\) comparing short course with standard duration for UTI in children.

A non-Cochrane meta-analysis found 22 studies that compared short-course antibiotics (up to 4 days) with 5 days or more for acute cystitis.\(^{35}\) The overall difference in cure rates between short and conventional courses of therapy was significant (6.4%; 95% CI 1.9–10.9%), favoring the conventional course. Similar results were obtained when only studies comparing the same agents in the short and conventional courses were included. Short-course amoxicillin was inferior to conventional-length course (difference in cure rate, 13%; 95% CI 4–24%). No difference was found between short-course and conventional-length courses of trimethoprim-sulfamethoxazole (difference in cure rate, 6.2%; 95% CI 3.7–16.2%).

A non-Cochrane meta-analysis compared short-course antibiotics (from a single dose to 3 days) with standard duration (7–14 days) for UTI in children.\(^{36}\) The meta-analysis found 16 studies, and concluded that long-course therapy was associated with fewer treatment failures. The difference remained significant if the analysis was restricted to studies of pyelonephritis. However, the review included single-dose treatment, which is used for acute cystitis in adult women. For studies that just compared 3-day therapy to long-course therapy, there was no significant difference in treatment failure or reinfection rates.\(^{36}\)

A Cochrane review excluded single-dose studies, and compared 2–4 days of antibiotics with 7–14 days for UTI in children (with or without systemic symptoms).\(^{37}\) The Cochrane reviewers identified 10 trials (652 children) with UTI. There was no significant difference in the frequency of positive urine cultures at 0–10 days after treatment. There was no significant difference between short- and standard-duration therapy in the development of resistant organisms, although there were trends to less resistance with short-course therapy at the end of treatment (one study: RR 0.57, 95% CI 0.32–1.01) or in recurrent UTI (three studies: RR 0.39, 95% CI 0.12–1.29). The reviewers conclude that a 2–4-day course of oral antibiotics appears to be as effective as 7–14 days in eradicating lower tract UTI in children.

**We conclude that short courses of antibiotics longer than 1 day (i.e., 2–4 days) are no less effective than standard duration (7–14 days), and**
can be recommended to treat uncomplicated UTI.

Aminoglycosides and UTI

Question | For children with UTI, is once daily administration of aminoglycosides compared with multiple daily dosing safer and more effective?

Literature review | We found four RCTs and a non-Cochrane meta-analysis.\(^{38}\)

A non-Cochrane meta-analysis compared once daily with multiple daily dosing of aminoglycosides in a number of different clinical situations. There were 24 studies, including four RCTs where aminoglycosides were used to treat UTI.\(^{38}\) Once daily dosing of aminoglycosides was at least as effective as multiple daily dosing, and was not associated with an increased incidence of oto- or nephrotoxicity. There was a suggestion of improved efficacy and reduced nephrotoxicity with once daily dosing in some trials. The available randomized evidence supports the general adoption of once daily dosing of aminoglycosides in pediatric clinical practice, to minimize cost, simplify administration, and to provide similar or even potentially improved efficacy and safety, compared with multiple dosing (see Appendix 2).

We recommend once daily dosing of aminoglycosides for treating children with acute UTI.

Empiric antibiotic treatment for cystitis

Any of the following regimens can be expected to cure the majority of acute cystitis (acute uncomplicated lower UTI without systemic symptoms, usually in girls > 2 years old):

cephalexin 25 mg/kg (max 1 g) orally, 8-hourly for 3 days OR
trimethoprim 4 mg/kg (max 150 mg) orally, 12-hourly for 3 days OR (if a trimethoprim liquid formulation is not available)
trimethoprim + sulfamethoxazole 4 + 20 mg/kg (max 160 + 800 mg) orally, 12-hourly for 3 days OR
amoxicillin + clavulanate 12.5 + 3.1 mg/kg (max 500 + 125 mg) orally, 12-hourly for 3 days

Empiric antibiotic treatment for acute pyelonephritis

For acute pyelonephritis (UTI with one or more systemic symptoms), we recommend either oral or IV therapy.

For initial oral therapy, we reviewed the literature and found 16 RCTs, which showed no significant differences in cure or relapse rates between many different oral antibiotics, including amoxicillin-clavulanate, cefaclor, cefadroxil, cefixime, cefprozil cephalexin, nitrofurantoin, and trimethoprim-sulfamethoxazole. Cefixime has been studied more thoroughly than other antibiotics. We recommend:

cefixime 4 mg/kg, orally, 12-hourly for 3 days OR
cephalexin 25 mg/kg (max 1 g) orally, 8-hourly for 3 days OR
amoxicillin + clavulanate 12.5 + 3.1 mg/kg (max 500 + 125 mg) orally, 12-hourly for 3 days OR
trimethoprim 4 mg/kg (max 150 mg) orally, 12-hourly for 3 days OR (if a trimethoprim liquid formulation is not available)
trimethoprim + sulfamethoxazole 4 + 20 mg/kg (max 160 + 800 mg) orally, 12-hourly for 3 days

Fluoroquinolones should not be used as first-line drugs, as they are the only orally active drugs available for infections due to Pseudomonas aeruginosa and other multiresistant bacteria.

If resistance to all the above drugs is proven, however, suitable alternatives are:
norfloxacin 10 mg/kg (max 400 mg) orally, 12-hourly for 3 days OR
ciprofloxacin 10 mg/kg (max 500 mg) orally, 12-hourly for 3 days

Treatment failures are usually due to a resistant organism, reinfection with a similar organism, or an unsuspected underlying abnormality of the urinary tract for which further investigations should be considered.

For initial IV therapy, we recommend:
gentamicin < 10 years: 7.5 mg/kg; ≥ 10 years: 6 mg/kg IV, daily PLUS
amoxi/ampicillin 50 mg/kg (max 2 g) IV, 6-hourly

In patients with penicillin allergy, gentamicin alone is usually effective.

Aminoglycosides are not recommended for patients with chronic renal failure. For such children, and in
other situations where it is recommended not to use an aminoglycoside (e.g., chronic liver disease, hearing or vestibular problems, and neuromuscular disease; see Appendix 2), we recommend:

- **Ceftriaxone 25 mg/kg (max 1 g) IV, daily** OR
- **Cefotaxime 25 mg/kg (max 1 g) IV, 8-hourly**

[NB: This regimen does not provide adequate cover for *P. aeruginosa* or enterococci, which are inherently resistant to these third-generation cephalosporins.]

We recommend switching to oral therapy when the child is improving, usually after 3 days but often longer for infants. We suggest continuing IV antibiotics until neonates and infants have settled, which may take 7–10 days.

A follow-up urine culture is advised at least 48 hours after the conclusion of therapy.

**Imaging following acute UTI**

Diagnostic imaging to look for VUR and scarring has been performed for many years, in an attempt to prevent progression to renal damage as a result of chronic pyelonephritis. The rationale has been that reflux plus infection may lead to renal scarring and chronic renal damage, and that preventing either reflux or infection or both might prevent renal damage.

There is no clear consensus in the literature regarding imaging following acute UTI in infancy. In the past, it has been common to recommend micturating cystourethrogram (MCUG) to identify vesicoureteric reflux, and ultrasound or 99mTc DMSA scan to identify renal tract anomalies and scarring.

**Question** | For a child presenting with a first UTI, can imaging of the urinary tract compared with no imaging identify children at risk of progressive renal damage?

**Literature review** | We found 73 observational studies, no RCTs, and two non-Cochrane systematic reviews of imaging techniques following UTI. We found a non-Cochrane meta-analysis of MCUG after UTI.

A non-Cochrane systematic review of routine diagnostic imaging following childhood UTI found 63 studies. All were descriptive, and only 10 were prospective. Another systematic review that included 73 studies also noted the many methodological limitations of the studies. The data did not support the use of less invasive tests such as ultrasound as an alternative to renal scintigraphy, either to rule out infection of the upper urinary tract or to detect renal scarring. Indeed, none of the tests accurately predicted the development of renal scarring. The reviewers concluded that the available evidence supports the consideration of contrast-enhanced ultrasound techniques for detecting VUR as an alternative to MCUG. They found no evidence to support the clinical effectiveness of routine investigation of children with confirmed UTI.

Neonates with UTI, particularly boys, have a high rate of structural abnormalities, and post-erior urethral valves need to be excluded. In one study, 22 of 45 male neonates with UTI had abnormal MCUG and/or ultrasound, although 19 of them had VUR alone.

There is a continuum and no clear cut-off between neonates and older infants in terms of the incidence of abnormal findings.

**Micturating Cystourethrogram**

VUR is found in 8–40% of children being investigated for their first UTI and is a known risk factor for recurrent UTI. A meta-analysis of patients found to have VUR by MCUG showed that a positive MCUG increases the risk of renal damage in hospitalized UTI patients by about 20%, whereas a negative MCUG increases the chance of no renal involvement by just 8%. VUR is, hence, a weak predictor of renal damage in pediatric patients hospitalized with UTI. The authors concluded that physicians should be aware of the limitations of using MCUG-detected primary VUR as an effective screening test for renal damage in this population. The pathogenesis of renal damage in such patients is probably complex because renal damage often occurs without demonstrable VUR. It is estimated that about half of all renal damage identified is due to congenital renal dysplasia and may not be amenable to interventions that are aimed to prevent further renal damage.

VUR has a strong familial component. The incidence of reflux in siblings was 26% in a cohort of asymptomatic siblings and 86% in siblings with a history of UTI, but <1% in the normal population. VUR tends to resolve with time: in a longitudinal study, 84% of children with UTI and VUR had spontaneous resolution after 5–15 years.

**Ultrasound**

Renal ultrasound is a poor predictor of VUR. In one prospective study of children aged 0–5 years,
ultrasound showed renal dilatation in only 17% of children found to have VUR by MCUG. However, missing mild-to-moderate reflux may not be important clinically, because the detection and treatment of lesser degrees of reflux has not been shown to confer benefit. One group has argued that the poor sensitivity of ultrasound to detect VUR may not matter. They found that only 16% of kidneys with VUR had associated scarring, and 50% of scarred kidneys were not associated with VUR. The authors concluded that MCUG provided little additional information to ultrasound.

Renal ultrasound will detect structural abnormalities of the kidneys (e.g., horseshoe kidney and duplex systems), and will detect obstructive lesions that result in dilatation of the bladder (e.g., post-erio urethral valves), kidneys, or ureters (e.g., pelviureteric junction and vesicoureteric junction obstruction).

Renal ultrasound in young children may require sedation, but is less invasive than MCUG. It is a sensitive screening tool for low-prevalence serious conditions with an effective intervention (surgery). It is widely available, cheap, and non-invasive.

99mTc DMSA scan

DMSA scintigraphy is the most sensitive technique for diagnosing renal scarring. A systematic review of imaging in childhood UTI suggested that renal scarring, diagnosed by intravenous pyelogram or DMSA scan, occurs in 5–15% of children within 1–2 years of their first diagnosed UTI. About a third of these scars are noted at the time of initial assessment, suggesting a high level of preexisting scarring, probably due to congenital renal dysplasia associated with high-grade VUR. DMSA scans often show transient abnormalities and are too sensitive to be performed routinely to detect clinically relevant parenchymal abnormalities.

Conclusion on imaging for child with UTI

We recommend that a routine ultrasound scan, if available, is performed on all neonates and children after their first UTI.

The need for further imaging will depend on the ultrasound result. If the ultrasound is normal, we do not recommend further imaging, because it is only likely to detect minor degrees of VUR (MCUG) or parenchymal abnormalities of little clinical significance (DMSA). If the ultrasound is abnormal, we recommend specialist consultation. Children with recurrent UTI may need further imaging to detect VUR and/or renal parenchymal defects (MCUG and/or DMSA scan), and specialist consultation on imaging is advised.

Preventing UTIs

Circumcision

Question | For boys with or without recurrent UTIs, does circumcision compared with no circumcision reduce the incidence of UTIs, and does circumcision cause harm?

Literature review | We found one RCT, seven case-control studies, four cohort studies, and a non-Cochrane systematic review.

A non-Cochrane systematic review analyzed data on 402,908 children. Circumcision was associated with a significantly reduced risk of UTI (OR 0.13, 95% CI 0.08–0.20) with the same odds ratio whatever the study design. The risk of UTI in normal boys is about 1%, so the number needed to treat (number of boys who would need to be circumcised to prevent one UTI) is 111. In boys with recurrent UTI or high-grade VUR, however, the risk of UTI recurrence is much higher at 10% and 30%, respectively, and so the respective numbers needed to treat are much lower at 11 and 4. About 2% of circumcisions are complicated by hemorrhage or infection.

We do not recommend routine circumcision merely to prevent UTIs. In contrast, we recommend considering circumcision in boys with recurrent UTIs, high-grade VUR, or anatomic abnormalities putting them at high risk of UTIs.

Preventing chronic renal damage

A systematic review of diagnostic imaging reported on four longitudinal studies of scarring that followed children for at least 2 years. New renal scars developed in 1.6–23% of children, and existing renal scars progressed in 6–34%. The highest rates of scarring were associated with the highest rates of recurrent UTI. Scarring tends to occur early: children <2 years old are at greater risk for scarring than are older children. In one study of children with normal DMSA scans at 3–4 years of age, 3% of 3-year-old and none of 179
4-year-old children developed scarring 2–11 years later, and 4 of the 5 who developed scarring had a history of ongoing recurrent UTI.\textsuperscript{51}

One long-term follow-up study in the UK found that progressive renal damage occurred in children with both renal scarring and VUR, or in children with either renal scarring or VUR followed by documented UTI.\textsuperscript{52} A combination of recurrent UTI, severe VUR, and the presence of renal scarring at first presentation is associated with the worst prognosis.\textsuperscript{2} On the other hand, a longitudinal study of children with primary VUR, identified after fetal renal pelvic dilatation was diagnosed by fetal ultrasound, found that children with grades I–III reflux had no progression of renal damage.\textsuperscript{52} Renal damage was strongly associated with grade IV–V reflux. Few children had UTI, and it appeared likely that most renal damage was due to pre-existing renal dysplasia rather than prior or ongoing UTIs.

**Prophylactic antibiotics**

**Question** | In children with a previous UTI, do long-term prophylactic antibiotics compared with no antibiotics or placebo reduce the frequency of recurrent UTIs, and do they prevent chronic renal damage? Is one antibiotic superior to other?

**Literature review** | We found eight RCTs, a Cochrane systematic review,\textsuperscript{55} and a non-Cochrane systematic review.\textsuperscript{54}

A Cochrane review\textsuperscript{33} identified eight “poor-quality” studies (618 children), of which five (406 children) compared prophylactic antibiotics with placebo or no antibiotics. The duration of antibiotic prophylaxis varied from 10 weeks to 12 months. Antibiotics reduced the risk of repeat positive urine culture compared to placebo or no treatment (RR 0.44, 95% CI 0.19–1.00). No side effects were reported. Few studies looked at the emergence of antibiotic resistance during prophylaxis.

The authors of the Cochrane review pointed out that only one study differentiated symptomatic UTI from screen-detected, asymptomatic UTI, yet few doctors would treat asymptomatic bacteriuria.\textsuperscript{53} They felt that the small number of poor-quality studies gave no reliable evidence of the effectiveness of antibiotics in preventing recurrent symptomatic UTI. They conclude that the evidence to support the widespread use of antibiotics to prevent recurrent symptomatic UTI is weak.\textsuperscript{53}

One study reported nitrofurantoin was more effective than trimethoprim in preventing recurrent UTI (RR 0.48, 95% CI 0.25–0.92), but patients receiving nitrofurantoin were more than three times as likely to discontinue the antibiotic due to side effects (mainly, gastrointestinal). Nitrofurantoin prophylaxis altered neither the pattern of resistance nor the bacteriologic constellation, while patients receiving trimethoprim prophylaxis had 76% trimethoprim-resistant bacteria during prophylaxis.\textsuperscript{55} Another study found that cefixime was as effective as nitrofurantoin in preventing recurrent UTI, but 62% of patients receiving cefixime and only 26% of patients receiving nitrofurantoin experienced an adverse reaction.\textsuperscript{56}

The author of a non-Cochrane review interpreted the same data differently.\textsuperscript{54} He concluded that prophylactic antibiotics seem to reduce recurrence of UTI. Because recurrent UTI is associated with new or progressive renal scarring in some children, he felt prophylaxis seemed sensible in two situations: (1) until a child’s risk level is known (preinvestigation), and (2) after a child has been shown to have renal damage or increased risk. He suggested continuing antibiotics until reflux had largely resolved.\textsuperscript{54}

A large, multicenter RCT published after both the above systematic reviews found that children with mild-to-moderate VUR randomized to prophylactic antibiotics had the same 1-year outcome as controls, who received placebo in respect to rate of recurrent UTI, type of recurrence, rate of subsequent pyelonephritis, and development of renal parenchymal scars.\textsuperscript{57}

We feel the evidence for or against prophylactic antibiotics is weak.

**We do not recommend prophylactic antibiotics for children with mild-to-moderate reflux following their first UTI.** For children with grade IV–V reflux, \textbf{we would recommend either commencing prophylaxis or waiting to see if the child has recurrence of UTI.}

If it is decided to use prophylactic antibiotics, we recommend:

nitrofurantoin 1–2.5 mg/kg (max 100 mg) orally, at night OR
trimethoprim 4 mg/kg (max 150 mg) orally, at 
night OR (if a trimethoprim liquid formulation is 
not available)

trimethoprim + sulfamethoxazole 4 + 20 mg/kg 
(max 160 + 800 mg) orally, at night OR

cephalexin 12.5 mg/kg (max 500 mg) orally, at 
night

17.2 Catheter-associated 
bacteriuria and UTIs

Treatment of catheter-associated 
bacteriuria and UTIs

In patients with urinary catheters, asymptomatic bac-
teriuria and pyuria are common. Positive cultures may 
represent colonization, not infection, and are unreli-
able unless taken through a newly inserted catheter. 
Giving antibiotics in this situation, including blad-
er irrigation with antibiotics, is likely to select for 
antibiotic-resistant organisms.

Urinary culture and treatment of positive cultures is 
recommended only if the patient has signs of systemic 
infeciton, such as fever or rigors, risk factors such as 
neutropenia or kidney transplant, or before urological 
surgery.

Catheter-associated candiduria

Isolation of Candida from the urine is common, partic-
ularly in association with indwelling urinary catheters, 
and in most patients, it represents only colonization. 
Antifungal therapy is not usually indicated. Removal of 
urinary tract catheters and stents is often helpful. There 
is no good evidence to support bladder irrigation with 
amphotericin B desoxycholate.38

Candiduria may rarely be the source of subsequent 
dissemination or a marker of disseminated candidia-
sis in high-risk patients. We recommend considering 
treatment of candiduria in symptomatic patients and 
patients with neutropenia.

If it is decided to treat high-risk patients with 
localized infection due to Candida albicans and other 
susceptible species, we recommend:

- fluconazole 6 mg/kg (max 300 mg) orally, daily 
  for 7 days

Relapse after treatment is frequent, and this likelihood 
is increased by continued use of a urinary catheter.

For treatment of resistant or non-albicans species of 
Candida, see Chapter 9.

Prevention of catheter-associated UTIs

Prophylactic antibiotics and 
catheter-associated UTIs

A Cochrane review of antibiotics in adults who were 
catheterized short-term found six parallel-group RCTs 
that met the inclusion criteria.59 There was weak evi-
dence that antibiotic prophylaxis, compared to giving 
antibiotics when clinically indicated, reduced the rate 
of symptomatic UTI in female patients after abdom-
inal surgery. There was limited evidence that giving 
antibiotics after surgery reduced the rate of bacteriuria, 
pyuria, and gram-negative isolates in patients’ urine, 
but the benefits are uncertain. There was also limited 
evidence that prophylactic antibiotics reduced bacteri-
uria in non-surgical patients.59 We found no studies in 
children.

We do not think the evidence is sufficient to jus-
tify giving prophylactic antibiotics to catheterized 
children.

Type of urethral catheter and 
catheter-associated UTIs

A variety of specialized urethral catheters have been 
designed to reduce the risk of infection, includ-
ing antiseptic impregnated catheters and antibiotic 
impregnated catheters. We found a Cochrane review of 
the effect of type of indwelling urethral catheter on the 
risk of UTI in adults who undergo short-term urinary 
catheterization.60 The review found 18 RCTs. Silver 
 alloy indwelling catheters reduced the risk of catheter 
acquired UTI, but are expensive, and the authors rec-
ommended further economic evaluation. They found 
that catheters coated with a combination of minocy-
cline and rifampin may also be beneficial in reducing 
bacteriuria in hospitalized men catheterized for less 
than 1 week, but this requires further testing. There 
was not enough evidence to suggest whether or not any 
standard catheter was better than another in terms of 
reducing the risk of UTI in hospitalized adults catheter-
ized short-term.

A Cochrane review found evidence from 17 
RCTs that suprapubic catheters have advantages 
over indwelling catheters in respect of bacteri-
uria, recatheterization, and discomfort.61 The clinical
significance of bacteriuria was uncertain, however, and there was no information about possible complications or adverse effects during catheter insertion.61

17.3 Intermittent catheterization and prophylactic antibiotics

Question | For children with neurogenic bladders using intermittent catheterization, do prophylactic antibiotics compared with giving antibiotics when clinically indicated reduce the frequency of UTIs or long-term renal tract morbidity?

Literature review | We found four RCTs and a Cochrane review.62

Children with neurogenic bladders are at risk of recurrent UTI, and often use intermittent catheterization. It is unclear whether prophylactic antibiotics are useful. A Cochrane review of urinary catheter policies found four trials, comparing antibiotic prophylaxis with giving antibiotics when microbiologically indicated.62 For patients using intermittent catheterization, there was limited evidence that receiving antibiotics reduced the rate of bacteriuria (asymptomatic and symptomatic). There was weak evidence that prophylactic antibiotics were better in terms of fewer episodes of symptomatic bacteriuria. A subsequent RCT found that prophylactic antibiotics were associated with an increased risk of UTI, perhaps due to selection of resistant organisms.63

We do not recommend prophylactic antibiotics for children with neurogenic bladder using intermittent catheterization.

References

In this chapter, we will not try to cover all virus infections in children. Instead, we will concentrate on some general principles and on those important virus infections not covered elsewhere in the book and where the diagnosis or management is controversial or difficult.

18.1 Diagnosing virus infections

Virus infections may be diagnosed clinically, by detecting the virus or by serology. A clinical diagnosis may be adequate in most circumstances for virus infections with a characteristic rash, such as chicken pox, or where a definitive diagnosis is not informative, such as a common cold. Viral culture is definitive, but often slow. It is possible, however, to speed up the diagnosis by initiating viral culture by placing a clinical specimen in tissue culture, and then using rapid viral techniques, such as immunofluorescence or polymerase chain reaction (PCR) on the tissue culture cells to diagnose specific infections, e.g., shell vial cultures for detecting cytomegalovirus (CMV) or other respiratory viruses. Other rapid techniques include techniques that can detect antigen in clinical specimens, such as immunofluorescence or ELISA, or that can detect viral nucleic acid, such as PCR. Rapid techniques are particularly useful when a rapid diagnosis is needed for decisions about antiviral treatment, e.g., herpes simplex virus (HSV) in the neonatal period, or for decisions about antibiotics and infection control, e.g., respiratory syncytial virus (RSV) infection.

Serology can be helpful in certain infections, but has limitations. Even newborns are capable of mounting an IgM response to some infections, e.g., CMV and rubella. Other viruses, however, elicit a delayed IgM response even in older children, so that the usefulness of an immediate serum specimen to detect specific IgM can be limited. IgG responses generally take 2–3 weeks, which is why acute and convalescent sera are sent. In general, serology is more useful in older children, who mount a more vigorous immune response. It is best to detect RSV by rapid techniques or even culture, while RSV serology is almost never clinically useful.

18.2 Cytomegalovirus

CMV is a herpesvirus, and as such can cause congenital infection and primary infection, and can establish a latent infection and reactivate, especially if there is altered cellular immunity.

Congenital CMV infection

Congenital CMV infection is the most common congenital infection (3–12/1000 live births). It is usually asymptomatic at birth, although 6–23% of asymptomatic and 22–65% of symptomatic babies with congenital CMV develop late sensorineural deafness. About 10% of congenitally infected babies are symptomatic at birth, with one or more of intrauterine growth retardation, microcephaly, periventricular calcification, purpuric rash due to thrombocytopenia, chorioretinitis, hepatosplenomegaly, and jaundice. The diagnosis is made by detecting CMV-specific IgM or by detecting CMV by viral culture or rapid diagnosis as early as possible, preferably within 1 week and certainly within 3 weeks of birth. This is because the incubation period for contracting CMV infection is 3–12 weeks. A retrospective diagnosis of congenital CMV infection can sometimes be made by using PCR to detect CMV DNA in dried blood on the filter paper from newborn screening cards.

Question  For babies with congenital CMV infection, does ganciclovir compared with no treatment improve outcome?

Literature review  We found case reports and observational studies (total 36 patients), two studies comparing doses (54 patients), one RCT (42 patients), and an overview.
All studies reported the use of IV ganciclovir for babies with symptomatic infection. The only RCT studied the effect of 6 weeks of IV ganciclovir, begun in the neonatal period, on hearing in 42 babies with central nervous system (CNS) infection.5 The study found that ganciclovir therapy prevented hearing deterioration at 6 months (none of 25 versus 7 of 17 or 41%), and may prevent hearing deterioration at 1 year.5 Almost two-thirds of treated infants, however, had significant neutropenia during therapy. There was one case report of a baby given IV ganciclovir followed by oral valganciclovir, to prevent hearing loss.7 There are no RCTs on the use of ganciclovir for liver disease or pneumonitis. The neurological prognosis and survival of congenital CMV with microcephaly or intracranial calcification is poor,8 which is important when making decisions about treatment. An overview concluded that studies of ganciclovir are promising but of insufficient number to make evidence-based recommendations about indications for treatment of congenital CMV.6

**Table 18.1** Treatment and prevention of opportunistic CMV infections.4–11

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ganciclovir 5 mg/kg IV, 12-hourly for 14–21 days</td>
<td>Ganciclovir 10 mg/kg IV, three times weekly or 5 mg/kg IV, five times weekly</td>
</tr>
<tr>
<td>Foscarnet 90 mg/kg IV, 12-hourly for 14–21 days (actual dose based on creatinine clearance; see product information)</td>
<td>Foscarnet 90–120 mg/kg/day IV, five times weekly (actual dose based on creatinine clearance; see product information)</td>
</tr>
<tr>
<td>Cidofovir 5 mg/kg IV, weekly for 2 weeks, given with probenecid and hydration (contraindicated if proteinuria &gt;2+ or creatinine clearance &lt; 55 mL/min)</td>
<td>Cidofovir 5 mg/kg IV every 2 weeks, given with probenecid and hydration OR 3 mg/kg IV, once weekly (contraindicated if proteinuria &gt;2+ or creatinine clearance &lt; 55 mL/min)</td>
</tr>
<tr>
<td>Valganciclovir 900 mg orally, 12-hourly for 14–21 days (for adolescents, no data in children)</td>
<td>Valganciclovir 900 mg orally, daily (for adolescents, no data in children)</td>
</tr>
</tbody>
</table>

We do not recommend ganciclovir routinely for all babies with congenital CMV infection. We recommend considering ganciclovir for babies with significant liver or lung disease from congenital or acquired CMV infection.

**ganciclovir 5 mg/kg IV, 12-hourly for 2–3 weeks**

**Acquired or reactivation CMV disease**

Being a herpesvirus, CMV can cause disease by primary infection or by reactivation, even in normal children. The presentation depends on age, and whether or not the child is immunocompromised. Most acquired CMV infection is asymptomatic or mild and self-limiting. Manifestations in normal children include rash and fever or a mononucleosis-like syndrome in adolescents. Patients with defects of T-cell immunity are at risk of retinitis, pneumonitis, and colitis. CMV infection is associated with graft rejection in renal transplant patients,9 and can cause severe disease in liver and bone marrow transplant patients and with human immunodeficiency virus (HIV) infection.

Treatment is not necessary in normal children, so recommendations about treatment and prevention apply essentially to immunocompromised children. There is no effective vaccine available. Prevention options include CMV immunoglobulin and long-term antiviral therapy. A Cochrane review of solid-organ transplant recipients found that prophylaxis with acyclovir, ganciclovir, or valacyclovir compared with placebo or no treatment significantly reduced the risk for CMV disease (19 trials; RR 0.42, 95% CI 0.34–0.52) and all-cause mortality (17 trials; RR 0.63, 95% CI 0.43–0.92), primarily due to reduced mortality from CMV disease.10 Treatment options include IV ganciclovir, oral valganciclovir, foscarternet, and cidofovir (see Table 18.1). We recommend specialist advice.

**18.3 Epstein-Barr virus (EBV)**

EBV is a herpesvirus, which is lymphotropic for B cells. EBV infection is often asymptomatic or unrecognized in infants and children. However, hospital-based series find that even very young children can present with an infectious mononucleosis-like syndrome, with fever, tonsilopharyngitis, lymphadenopathy, and hepatosplenomegaly.12,13 Young children are more likely to have skin rash and upper eyelid edema than older children,12 whereas older children are more likely to develop hepatitis.11 Marked lymphocytosis with atypical lymphocytes is a consistent hematologic finding in all age groups.11 Neurological manifestations include meningitis, meningoencephalitis, including
Viral infections

...the “Alice in Wonderland syndrome” (distortion in body image characterized by enlargement, diminution, or distortion of part or of the whole body, which the person knows is not real), cerebellitis, Guillain–Barré syndrome, and facial nerve palsy. EBV can replicate in B cells, which viral replication is normally controlled by T cells and natural killer cells. EBV is oncogenic: it can cause Burkitt lymphoma, B-cell lymphoma (particularly in association with HIV infection), and nasopharyngeal carcinoma, and can disseminate to cause a lymphoproliferative syndrome in children post-transplant and children born with X-linked lymphoproliferative syndrome.

Although acyclovir has in vitro activity against EBV, it has little activity in vivo. It has not been shown to reduce symptoms of EBV infection in RCTs, although in one of the studies acyclovir plus prednisone did reduce viral shedding. Valacyclovir and ganciclovir have had no clinical or virologic effect in studies.

Parenteral corticosteroids are often recommended if there is imminent airways obstruction, although without formal evidence. We found no studies on the effect of corticosteroids on airways obstruction. We found one RCT on the effect of dexamethasone on pain in exudative tonsillitis due to infectious mononucleosis. A single dose of dexamethasone 0.3 mg/kg (max 15 mg), orally, reduced pain at 12 hours, but not later. We found an observational study that reported that corticosteroids were given to 45% of patients with EBV infection, although only 8% qualified based on traditional criteria.

18.4 Herpes simplex virus

HSV is a double-stranded DNA herpesvirus. There are two major serotypes, HSV-1 and HSV-2.

Neonatal HSV

Neonatal HSV carries a high mortality if untreated. It is uncommon, with an incidence from 1 in 2500 live births in the USA to 1 in 60,000 in the UK. HSV-1 is now responsible for around 50% of cases. Neonatal HSV infection is acquired during the birth process in about 85% of cases, as the neonate comes in contact with the virus during passage through an infected birth canal. Infection is probably post-natally acquired from contact with infected oral secretions from a caregiver in the remaining 15% of cases.

Neonatal infection most commonly follows primary maternal genital HSV, because the baby is exposed to a high viral inoculum before there has been maternal seroconversion producing transplacental maternal IgG antibody that would protect the baby. Neonatal infection less commonly follows reactivation of maternal genital HSV when the high viral load presumably swamps any maternal antibody. The risk of neonatal infection is 33–50% if the mother develops primary genital HSV, and some authorities recommend empiric acyclovir for the baby of a mother with known primary genital HSV around delivery. Cesarean section reduces but does not eliminate the risk of neonatal infection in this setting. However, only about a quarter of all women with primary genital HSV are themselves symptomatic at delivery.

If a woman with recurrent genital HSV without visible genital lesions is shedding the virus, the risk to the baby is <5%. True congenital HSV infection from intrauterine transfer with chorioretinitis, microcephaly, and skin lesions at birth is seen in <5% of cases.

Neonatal HSV disease usually presents in the first 3 weeks, but can be anything from day 1–4 weeks. Infection can manifest as localized disease, pneumonitis, encephalitis, or disseminated disease. About half the babies now present with disease localized to the skin, eye, or mouth (SEM disease), with one or more of skin vesicles, conjunctivitis, and vesicles in the mouth. Viral pneumonitis with onset at 3–5 days is another recognized presentation, and early suspicion of the diagnosis is critical to outcome. Disseminated HSV presents at about 1 week of age with fever, shock, disseminated intravascular coagulopathy, jaundice with hepatitis, and sometimes with seizures from encephalitis.

If localized HSV infection or pneumonitis is recognized and treated early, the prognosis is relatively good, with 10% long-term morbidity. If not, the risk of dissemination is as high as 70%. Even with modern antiviral therapy, the mortality for babies with encephalitis is 15%, and over 65% of survivors have significant neurological impairment. For children with disseminated multiorgan disease, the mortality approaches 50% and over 50% of survivors have severe neurological impairment.

Diagnosis needs to be made urgently, usually by rapid viral techniques, such as immunofluorescence or PCR on fluid from a vesicle, swabs from eyes or...
nasopharynx, and cerebrospinal fluid. If the baby has pneumonitis, a rapid diagnosis can be made using immunofluorescence or PCR on secretions from a nasopharyngeal or endotracheal aspirate. Serology is generally unhelpful in acute diagnosis. If rapid diagnosis is not available and HSV is suspected, we recommend taking samples for viral cultures and serum for HSV-specific IgM and treating empirically. Pharmacokinetic studies have shown that a high dose of acyclovir is needed for neonates.22 We recommend:

acyclovir 20 mg/kg IV, 8-hourly (14 days for localized disease, 21 days for encephalitis or disseminated disease)

Primary HSV gingivostomatitis
Primary HSV infection can be asymptomatic, or can cause herpetic gingivostomatitis or genital herpes. Gingivostomatitis means inflammation of the gums and mouth. It mainly affects children aged 6 months to 2 years. The main features are painful ulcers on the gums, tongue, and pharynx, often with satellite vesicular lesions on the lips and cheeks where the child dribbles. The child is febrile, miserable, and drools saliva, which cannot be swallowed because of pain. There is often edema of the mouth and neck, and tender submandibular lymphadenopathy. The condition is extremely painful.23

We found one RCT, in which children with primary herpetic gingivostomatitis were randomized to acyclovir suspension 15 mg/kg (max 200 mg) five times a day for 7 days, or placebo.24 Children receiving acyclovir had oral lesions for 4 days compared with 10 days for placebo, and had shorter duration of fever (1 versus 3 days), extraoral lesions around the mouth (0.0 versus 5.5 days), eating difficulties (4 versus 7 days), and drinking difficulties (3 versus 6 days). Viral shedding was significantly shorter in the group treated with acyclovir (1 versus 5 days).22 The per kilogram dose of acyclovir in the study24 is somewhat higher than that recommended by pharmacokinetic studies, and the maximum dose is lower.25,26

For treatment, depending on whether or not the child can drink, we recommend:

acyclovir 10 mg/kg (max 400 mg) orally, five times daily for 7 days OR
acyclovir 10 mg/kg (max 400 mg) IV, 8-hourly, until drinking, then oral as above

Recurrent herpes simplex labialis
(cold sores)
About 20–40% of adults have recurrent cold sores, but onset is often in childhood.21,27 Cold sores arise due to reactivation of chronic, latent HSV-1 infection from the ganglion of the trigeminal nerve, which can be spontaneous or precipitated by stress.27 The frequency can range from more frequently than monthly to occasional cases every few years. Cold sores occur at the border of the lip and the skin.27 Aphthous oral ulcers occur within the mouth and may be confused with recurrent mucosal herpetic lesions, but should not be confused with cold sores because of their position.28 If necessary, a swab for HSV immunofluorescence and/or culture will confirm HSV infection.

Studies of topical agents have shown that early treatment can be effective. An RCT found that 15% idoxuridine in dimethyl sulfoxide (DMSO) cream shortened pain by 1.3 days and time to healing by 1.7 days.29 Topical acyclovir ointment is ineffective in immunocompetent adults. However, both acyclovir cream30 and topical penciclovir,31,32 which is the prodrug for famciclovir, penetrate better and reduce the duration of lesions statistically significantly, but only by about 0.5 day.30–32 Topical therapy has not been associated with significant resistance to antivirals.33 The use of an iontophoretic applicator to improve skin penetration of topical acyclovir reduced the duration of lesions by 1.5 days in an RCT.34

Oral antivirals are effective, but frequent use is expensive and risks selecting for resistant HSV. A single dose of valacyclovir in adults reduces the duration of cold sores by 1 day.35 Valacyclovir has not been studied in children.

We recommend that, if possible, acyclovir be given at the first sign of a recurrence, using an iontophoretic applicator. We recommend:

acyclovir 5% cream topically, 4-hourly while awake, for 5 days OR
penciclovir 1% cream topically, 2-hourly while awake, for 4 days OR
15% idoxuridine in DMSO cream, 3-hourly while awake, for 4 days

Prevention of recurrent HSV skin infections
For prevention of extremely frequent skin recurrences, we found only one RCT, a double-blind crossover study
in adults with recurrent cold sores.\textsuperscript{36} Regular oral acyclovir 400 mg 12-hourly reduced the mean number of recurrences per 4-month treatment period from 1.80 to 0.85 episodes per patient, and the mean number of virologically confirmed recurrences from 1.40 to 0.40 per patient.\textsuperscript{36} There were no adverse events, although resistance was not studied. There are concerns about acyclovir resistance and expense with prolonged use, and the benefits are modest. We recommend only prophylactic oral acyclovir for children with extremely frequent and debilitating recurrences of HSV skin infections:

\textbf{acyclovir 10 mg/kg (max 400 mg) orally, 12-hourly}

\textbf{Genital HSV}

For primary genital herpes and for recurrent genital herpes, see p. 218.

\textbf{Eczema herpeticum}

Eczema herpeticum is a widespread HSV infection of inflamed skin, most often occurring in patients with atopic dermatitis.\textsuperscript{37} It is sometimes called Kaposi’s varicelliform eruption, but is caused by HSV, not varicella. Although it is sometimes suggested that it may result from excessive use of topical corticosteroids, a large retrospective review suggested that undertreatment of atopic dermatitis is a greater factor.\textsuperscript{38} The HSV infection is equally likely to be primary or recurrent.\textsuperscript{38}

The characteristic clinical pattern is an eruption of dome-shaped blisters and pustules in the eczematous lesions, along with severe systemic illness with fever and lymphopenia.\textsuperscript{38} The diagnosis is made by immunofluorescent staining of skin swabs or PCR or culture.

Eczema herpeticum can be severe. Depending on severity, we recommend:

\textbf{acyclovir 10 mg/kg (max 400 mg) orally, five times daily for 7–14 days OR}

\textbf{acyclovir 10 mg/kg (max 400 mg) IV, 8-hourly, until drinking, then oral as above}

\textbf{HSV infection in immunocompromised children}

Immunocompromised children with defective T-cell function are at risk of severe and recurrent HSV infections. These are usually severe, local, mucocutaneous, or skin lesions, although disseminated infection with visceral or CNS involvement can occur.\textsuperscript{39} Oral acyclovir is highly effective at preventing HSV infections in immunocompromised children.\textsuperscript{40} If HSV infections do occur in immunocompromised children, we recommend treating for longer:

\textbf{acyclovir 10 mg/kg (max 400 mg) orally, five times daily for 14 days OR}

\textbf{acyclovir 10 mg/kg (max 400 mg) IV, 8-hourly, until drinking, then oral as above}

\textbf{18.5 Measles}

Measles is an acute viral infection that is responsible for an estimated 800,000 deaths annually, almost all being children in developing countries.\textsuperscript{41,42} The live attenuated vaccines are highly effective, so measles is a vaccine-preventable disease. Furthermore, measles affects only humans, and the vaccine is effective against all strains, so global elimination of measles is possible.\textsuperscript{42}

In developing countries, the diagnosis is made clinically. In Brazil, where measles is common, a clinical case definition had 100% sensitivity compared with serum IgM.\textsuperscript{43} In industrialized countries, where occasional cases of measles occur following introduction by a traveler or an unimmunized person, clinical diagnosis is far less reliable.\textsuperscript{44} In this setting, a clinical diagnosis should be confirmed either by antigen detection (detecting measles virus antigen in nasopharyngeal secretions using an immunofluorescent stain) or by detecting serum IgM to measles. Immunization also causes a raised measles-specific IgM, so if a child who has recently been immunized against measles develops a suspicious rash, a raised serum IgM to measles does not distinguish between vaccine-acquired and wild-type measles.

There is no specific treatment for measles virus infection. In developing countries, children die because of acute measles pneumonia often complicated by secondary bacterial pneumonia, acute encephalitis, or because of immunosuppression that follows measles and leaves the child susceptible to diarrheal diseases for up to a year post-measles.\textsuperscript{41,42} Children with HIV infection develop more severe measles and are more likely to die from measles.\textsuperscript{45}

\textbf{Treatment of measles}

\textbf{Measles and vitamin A treatment}

It has been suggested that children in developing countries with low serum levels of retinol (vitamin A) who develop measles might benefit from being given
vitamin A acutely. An RCT from South Africa found that 92% of children admitted with severe measles had low serum retinol levels. Those randomized to receive retinyl palmitate (200,000 IU orally, daily for 2 days) recovered more rapidly from pneumonia and diarrhea, had less croup, and spent fewer days in the hospital. Of the 12 children who died, 10 were among those given placebo ($p = 0.05$). Overall, the risk of death or a major complication during the hospital stay was halved in children treated with vitamin A.46

A Cochrane review found eight RCTs of the use of vitamin A in acute measles.47 There was no significant reduction in the risk of mortality in the vitamin A group when all the studies were pooled (RR 0.70, 95% CI 0.42–1.15). Using two doses of vitamin A (200,000 IU) on consecutive days was associated with a reduction in the risk of mortality in children <2 years old (RR 0.18, 95% CI 0.03–0.61) and a reduction in the risk of pneumonia-specific mortality (RR 0.33, 95% CI 0.08–0.92). The three studies using two doses were from areas where case fatality was more than 10%. There was no evidence that vitamin A in a single dose was associated with a reduced risk of mortality among children with measles. There was a reduction in the incidence of croup (RR 0.53, 95% CI 0.29–0.89), but no significant reduction in the incidence of pneumonia (RR 0.92, 95% CI 0.69–1.22) or diarrhea (RR 0.80, 95% CI 0.27–2.34) with two doses. There were no trials that directly compared a single dose with two doses. There has been no toxicity shown from this dose of vitamin A. Vitamin A given to vitamin A-deficient children with acute measles in Zambia reduces the risk of measles-related pneumonia.48

There has been only one study in an industrialized country, an RCT of 105 children in Japan that showed that vitamin A was associated with a reduction in duration from cough from 9.2 to 7.2 days, without toxicity.49

We support the WHO recommendation50 that two doses of vitamin A (200,000 IU) be given to all children with measles in developing countries, especially to children under the age of 2 with severe measles, in addition to the standard management. For acute measles in a developing country, we recommend:

**vitamin A (200,000 IU) orally, daily for 2 days**

**Measles and antibiotics**

Measles virus can cause severe viral pneumonia, but children with measles are also at risk of developing bacterial pneumonia due to immunosuppression and superinfection. We found surprisingly few studies on the bacteria causing pneumonia in measles. One study performed endotracheal aspirates in children with measles, not the ideal specimen because the organisms grown may not be causing the pneumonia. Some of the organisms were probably commensals (e.g., *Streptococcus viridans*), but the study authors also reported growing Gram-negative bacilli, *Staphylococcus aureus* and *Streptococcus pneumoniae*, which are more likely to have been pathogens.51

Treating children with severe measles pneumonia with antibiotics empirically might save lives. In a study designed to detect and treat pneumonia according to a WHO decision strategy, children in Nepal with a WHO clinical diagnosis of pneumonia were treated at home with 5 days of oral co-trimoxazole.52 By the third year of the program, there was a 28% reduction in all-cause mortality, particularly among infants. In addition to reduction in deaths due to pneumonia, there was a significant reduction in deaths due to diarrhea and measles, indicating that reduction in pneumonia morbidity had considerable carryover effect. The longitudinal, observational nature of the study52 does not provide strong evidence that empiric antibiotics improve mortality in measles.

A Cochrane review looked at all trials of antibiotics for children with measles, not just those with measles pneumonia.53 Six trials with 1304 children were included. The reviewers felt that the quality of the trials reviewed was poor. All the trials were unblended except one, and randomization was either not described or was by alternate allocation. Four of the 764 children given antibiotics died compared with 1 of the 637 controls. The reviewers concluded that there was very weak evidence for giving “prophylactic” antibiotics to all children with measles, and that available evidence suggests that antibiotics should be given only if a child has clinical signs of pneumonia or other evidence of sepsis.53 The Cochrane review has been withdrawn because the authors do not have time to update it. At least one writer has argued passionately that it is vitally important to perform RCTs to see whether or not all children with measles in developing countries should be given antibiotics, because the disease is so common with such a high mortality that if they are effective, prophylactic antibiotics could have a profound effect on outcome.54 This letter writer feels that
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the existing evidence from the Cochrane review of controlled trials suggests that prophylactic antibiotics are likely to reduce serious morbidity, and he argues that children in developing countries with measles should be given prophylactic antibiotics. If it is decided to give antibiotics to a child in a developing country with measles, the choice may depend on availability, but we would advise antibiotics with activity against *S. aureus* and *S. pneumoniae* (see p. 188).

**Micronutrients and measles**

There is evidence from RCTs that giving antioxidants, vitamin C and vitamin E, or giving zinc does not improve the outcome of children with measles and pneumonia.

**Prevention of measles**

**Measles immunization**

Vaccine is the most effective way of preventing measles, and has been shown to be one of the most cost-effective public health interventions available. Current measles vaccines use live, attenuated measles virus. They are generally contraindicated in immune-deficient children. Because measles is more severe in HIV infection and is common in developing countries, however, and because severe adverse events from measles vaccine are rare, it is recommended that HIV-infected children be immunized routinely with measles or measles–mumps–rubella (MMR) vaccine unless they are severely immunocompromised (defined as CD4 count <750 cells/μL or 750 × 10^9/L if <12 months, <500 aged 1–5 years, <200 aged >5 years; see Chapter 8).

In industrialized countries, because maternal antibody interferes with the response, the proportion of children responding to measles immunization depends on age. In the USA, 98% of children aged 15 months seroconverted to measles, compared with 95% vaccinated at 12 months and 87% vaccinated at 9 months. There is a trade-off between early protection and the proportion seroconverting. In industrialized countries, the first dose of measles vaccine with or without mumps and rubella is given at 12–15 months. A booster is usually recommended at 5–12 years to improve coverage. In developing countries, in contrast, the first dose is recommended at 9 months because the morbidity and mortality are higher in the first year of life.

**Measles post-exposure prophylaxis**

It is currently recommended that unimmunized or immunocompromised household and other close measles contacts be given measles vaccine or MMR within 72 hours of exposure or normal human immunoglobulin within 6 days of exposure, to prevent measles or reduce the severity. Immunoglobulin is recommended for those who are least likely to respond to vaccine (infants <1 month), for those who might get disseminated disease from the vaccine (severely immunocompromised persons), and for pregnant women (because of the potential but unknown risk of the vaccine to the fetus). The evidence for these recommendations is sparse. In a measles outbreak in California, primary measles immunization was 95% protective against infection; i.e., previously immunized children were well protected. In contrast, it was not possible to show that either post-exposure vaccination (protection 4%) or immunoglobulin (protection 8%) prevented infection, although severity of measles was not measured, so either vaccine or immunoglobulin may have reduced severity. A Japanese study found that commercially available normal human immunoglobulin had variable measles antibody titers, and 57% of children receiving immunoglobulin with a titer of 16 IU/mL or lower developed clinical measles.

Primary immunization is clearly superior to secondary prevention.

**Prophylactic vitamin A and measles**

There is good evidence that vitamin A improves outcome when given to children with acute measles.
Mainly on this basis, the WHO has recommended vitamin A prophylaxis be given at the time of immunization to children in developing countries when vitamin A deficiency is likely. It has been argued that prophylactic vitamin A, which is extremely cheap, will reduce mortality from diarrhea and reasonable evidence that it will reduce mortality from measles and malaria.65

We could find no convincing evidence that vitamin A supplementation prevents diarrhea (see p. 81). We found one study suggesting that vitamin A supplementation was associated with lower measles antibody titers,66 although a subsequent study found that vitamin A-supplemented children had equal or higher measles titers.67 An RCT in Ghana found a lower incidence of measles in vitamin A-supplemented children (23.6/1000 child-years) than in children given placebo (28.9/1000 child-years), but the difference was not statistically significant69 and measles case fatality was no different (15.4% versus 14.5%, respectively).69 A large RCT in Ghana, India, and Peru found that vitamin A supplementation was safe, but had no measurable benefits in terms of severe morbidity or mortality.70

18.6 Varicella zoster virus (VZV)

VZV is a herpesvirus that can cause primary infections (varicella or chicken pox) and can reactivate (zoster or shingles). The name is confusing; it used to be thought that varicella virus and herpes zoster were different viruses causing different syndromes, and VZV is a composite name.

Chicken pox

Most chicken pox is mild, but because almost all children get chicken pox and occasional cases are severe, the overall effect in terms of morbidity and mortality of chicken pox in an unimmunized population is great.71,72

Recovery from VZV is dependent on cellular (T-cell) immunity. Chicken pox and zoster are both far more severe in immunocompromised patients with defective T-cell immunity. In contrast, boys with X-linked agammaglobulinemia who cannot make antibodies recover normally from acute chicken pox. Nevertheless, previously healthy children with no demonstrable immunodeficiency sometimes get severe and even fatal chicken pox.71,72

Diagnosis in primary care is usually clinical. When definitive diagnosis is important, the most useful technique is rapid diagnosis using immunofluorescent staining to detect antigen in scrapings of lesions. PCR, if available, is highly sensitive.73 Antibody testing for specific IgM is less reliable, while viral culture and a rise in specific IgG both give delayed results.

Antiviral treatment of varicella

Antiviral treatment is not recommended routinely in normal, otherwise healthy children with varicella.74,75 In a placebo-controlled RCT, previously healthy children with varicella given acyclovir defervesced sooner than the placebo group (median 1 versus 2 days), their lesions healed quicker (median 3 versus 2 days), and they had fewer skin lesions (median 500 versus 336). However, acyclovir did not significantly change the rate of complications of varicella (10% versus 13.5%), and acyclovir recipients had lower geometric mean serum antibody titers to VZV than their placebo counterparts 4 weeks after the onset of illness, suggesting acyclovir may impair the immune response.76 The modest benefits do not justify the cost, possible adverse effects, and risk of acyclovir resistance.

Antiviral therapy should be reserved for children with or at risk of severe disease, and the dose and route should be determined by the circumstances, such as the age and immune status of the child, and the timing and severity of infection.74,75

In immunocompromised patients with significant T-cell deficiency, with or without severe chicken pox, and in normal patients with complications of varicella (e.g., pneumonitis or encephalitis), we recommend:

acyclovir 10 mg/kg IV, 8-hourly until all lesions crusted and healed (usually 7–14 days)

Zoster (shingles)

Zoster (herpes zoster, shingles) is caused by reactivation of VZV from where it lies dormant in dorsal root ganglia. Generally, primary varicella tends to occur in childhood, whereas herpes zoster is a disease of adults, with most patients being over 45 years old.77,78 The age-adjusted incidence rates of herpes zoster are lowest (0.45/1000 person-years) in children 0–14 years of age and highest (4.2–4.5/1000 person-years) in people 75 years and older.79 In the pediatric population, the incidence is lowest from 0 to 5 years of age (20/100,000 person-years) and highest in adolescents (63/100,000 person-years).80
Antigen-specific T cells are believed to be the principal gatekeepers of latent VZV. Conditions in which cellular responses are lost or diminished by immunosuppression pose a risk for reactivation of VZV and recurrent disease manifestation as herpes zoster. Herpes zoster in the elderly is associated with loss of VZV-specific cellular immunity. Zoster in children is particularly associated with immunosuppression due to chemotherapy or HIV infection. The mechanism in chemotherapy is suppression of cellular immunity, whereas zoster occurs in HIV infection due to viral destruction of T cells.

Acquisition of herpes zoster in healthy immunocompetent children in early childhood or during intrauterine exposure has been attributed to immaturity of the immune system. If zoster occurs in a previously well child whose physical examination is normal apart from the rash, the child almost never has an underlying malignancy or other systemic disease. There is an association between maternal chicken pox in pregnancy and the child developing zoster in the first year of life. Zoster in infancy can also follow post-natal chicken pox. It has been suggested that in infancy the presence of maternal antibody modifies primary infection and that subclinical primary infection may predispose to herpes zoster.

Post-herpetic neuralgia is age dependent. In a large, observational study, severe post-herpetic neuralgia occurred only in adults >60 years old. For patients <50 years old, only 1.5% had mild pain after 3 months and 98.5% had no pain. Zoster almost never causes post-herpetic neuralgia in children. In an observational study of 118 children and adolescents with 121 episodes of zoster, no child had pain after 1 month, even though none received antivirals.

Ophthalmic zoster is potentially sight-threatening at any age. Without antiviral therapy, approximately 50% of patients will have ocular complications (e.g., keratopathy, episcleritis, iritis, or stromal keratitis), some of which are potentially sight-threatening. Oral antiviral therapy reduces the frequency of late ocular complications from about 50% to 20–30%. Systemic antivirals are advisable in severe cases. It is advised that patients with herpes zoster ophthalmicus should be evaluated by an ophthalmologist who is experienced in the management of corneal diseases.

Antivirals are also recommended for immunosuppressed children with zoster, as zoster infection can be fatal.

We do not recommend antivirals for immunocompetent children with zoster.

For immunocompromised children with zoster and for any child with ophthalmic zoster, we recommend antivirals. The route and duration will depend on severity and risk, which is a function of degree of immunosuppression. We recommend:

- acyclovir 10 mg/kg (max 400 mg) IV, 8-hourly (until healed, usually 7–14 days) OR acyclovir 20 mg/kg (max 800 mg) orally, five times daily OR famciclovir 250 mg orally, 8-hourly (>12 years) OR famciclovir 500 mg orally, 8-hourly (>12 years and immunocompromised) OR valacyclovir 1 g orally, 8-hourly (>12 years)

Prevention of varicella zoster infections

Immunization against VZV

It is possible to reduce the incidence of varicella using universal childhood immunization with live, attenuated VZV vaccines, and this has been shown to reduce morbidity and mortality in the USA. It is controversial whether or not universal varicella vaccine is cost-effective. Because of the relatively high cost of the vaccine, a number of cost-effectiveness analyses have found that the cost-effectiveness is marginal. Universal VZV vaccine has been introduced in Australia, as well as the USA. In the UK, universal VZV vaccine has been opposed because mathematical modeling suggests that universal VZV vaccine might lead to a temporary rise in zoster in the elderly. This is because elderly persons in contact with young children have less zoster than those with less contact, which has been interpreted as being due to natural boosting of immunity from children with chicken pox (although other interpretations of the reason for reduced zoster are possible, such as the emotional benefits of contact with children).

In countries without universal immunization, individuals can be protected by the use of VZV vaccine from 1 year. This is only about 85% protective against infection, but virtually 100% protective against severe varicella.
VZV vaccines are not recommended usually for children with immunodeficiency. The vaccine has been shown, however, to be safe and immunogenic in children with HIV infection, who are not profoundly immunosuppressed (CD4 count > 200/μL)\(^ {105,106}\) (see Section 8.5, p. 107).

VZV vaccine is recommended for susceptible health-care workers, provided they are not immunocompromised.\(^ {107}\)

Post-exposure prophylaxis against varicella zoster infection
Varicella is spread by air and is highly infectious, although the duration and nature of exposure that constitute a significant risk are unknown and controversial. About 90% of non-immune household contacts develop varicella.\(^ {107}\) Possible ways to prevent or ameliorate varicella infection post-exposure are by active immunization with varicella vaccine, by passive use of immunoglobulin or by using antivirals.

Post-exposure immunization with VZV vaccine
Data from the USA and Japan from household, hospital, and community settings indicate that varicella vaccine is effective in modifying varicella severity if used up to 3 days, and possibly up to 5 days after exposure.\(^ {108−111}\) In an RCT,\(^ {111}\) 22 children given VZV vaccine following household exposure had the same rate of varicella infection as 20 children given placebo (RR 1.1, 95% CI 0.55–2.21), but the risk of developing moderate to severe disease was eight times greater in the placebo group, indicating an 80% protective effect against moderate to severe disease.\(^ {111}\)

The US Advisory Committee on Immunization Practices recommends the use of VZV vaccine in susceptible persons aged 1 year or older following exposure to varicella.\(^ {107}\) If exposure to varicella does not cause infection, post-exposure immunization should induce protection against subsequent exposure. If the exposure results in infection, there is no evidence that administration of VZV vaccine during the presymptomatic or prodromal stage of illness increases the risk for vaccine-associated adverse events.\(^ {111}\)

Post-exposure immunoglobulin for protection against varicella
Immunoglobulin with high-titer antibodies against VZV provides passive protection against varicella, and is most useful when active immunization is likely to be ineffective or dangerous because of age (e.g., neonates, high-risk infants <1 year old) or impaired T-cell immunity. Immunoglobulin is expensive, in scarce supply, and provides only temporary protection. It should be given only to prevent varicella in exposed patients who cannot be given VZV vaccine.

Studies conducted in 1969 indicated that zoster immune globulin (ZIG), which is prepared from patients recovering from herpes zoster and contains high levels of VZV antibody, prevented clinical varicella in susceptible, healthy children if administered within 72 hours of exposure.\(^ {112}\) ZIG also lowered attack rates among immunocompromised persons if administered no later than 96 hours after exposure.

Varicella zoster immune globulin (VZIG; prepared from plasma obtained from healthy, volunteer blood donors who are identified by routine screening to have high antibody titers to VZV) became available in 1978. Both serologic and clinical evaluations have demonstrated that the product is equivalent to ZIG in preventing or modifying clinical illness in susceptible, immunocompromised persons who are exposed to varicella.

Subsequent studies have shown that, like VZV vaccine, ZIG does not always prevent infection but does reduce the severity in immunosuppressed household contacts\(^ {113}\) and in neonates whose mothers have perinatal chicken pox.\(^ {114}\)

The duration of protection is unknown, but should be at least one half-life or approximately 3 weeks. It is recommended that susceptible high-risk persons for whom varicella vaccination is contraindicated and who are again exposed 3 weeks or more after a dose of VZIG should receive another full dose of VZIG.\(^ {107}\)

VZIG has no effect in treating clinical varicella or herpes-zoster infection.\(^ {107}\)

We do not recommend treating children with active chicken pox or zoster with ZIG.

VZIG is supplied in 125 U and 625 U vials. The recommended dose is 125 U/10 kg, up to a maximum of 625 U. The minimum dose is 125 U; fractional doses are not recommended. VZIG should be administered intramuscularly as directed by the manufacturer, and never intravenously.
VZIG prophylaxis is generally recommended for certain groups of children at high risk of severe varicella, shown in Box 18.1, and the rationale is discussed below.

**Box 18.1 Children for whom prophylaxis with ZIG is recommended** following significant exposure.

- Neonate whose mother develops chicken pox 5 days or fewer before delivery (some say 7 days or fewer) to 2 days after delivery
- Premature infants < 28 weeks’ gestation or who weigh 1000 g or less at birth, regardless of maternal history
- Premature infants 28 weeks’ gestation or more with no history of maternal chicken pox or no VZV-specific IgG
- Immunocompromised child (with impaired T-cell immunity), with no prior history of varicella or VZV immunization and no VZV-specific IgG
- *The definition of a significant exposure to VZV is controversial, and not based on strong evidence.*

**Neonates and VZIG**

The attack rate in healthy neonates is highest in babies exposed to maternal chicken pox, when transmission is mainly transplacental. Neonates whose mothers develop chicken pox 5 days or fewer before delivery and up to 2 days after birth are the highest risk group, because the babies are exposed to large amounts of virus before maternal IgG can cross the placenta. The neonatal mortality was as high as 30% for untreated babies, who developed neonatal chicken pox after being exposed to maternal chicken pox in this high-risk time period. The advent of VZIG has changed this. The rate of neonatal chicken pox in babies given VZIG after birth is 30–40%, which is not substantially different from neonates not given VZIG. However, the occurrence of complications and fatal outcomes is substantially lower for neonates who are treated with VZIG than for those who are not, and VZIG is recommended for high-risk neonates. VZIG is probably not necessary for neonates whose mothers develop varicella more than 5 days before delivery, because those infants should be protected from severe varicella by transplacentally acquired maternal antibody, although some authorities extend the recommendation for VZIG out to 7 days before delivery, because antibody levels in the baby are sometimes low if mother’s varicella was within 7 days.

Transmission of varicella to neonates in the hospital nursery following post-natal exposure is rare, because most neonates are protected by maternal antibody. Premature infants who have substantial post-natal exposure should be evaluated on an individual basis. The risk of post-natally acquired varicella in premature infants is unknown. Because the immune systems of premature infants may be compromised, administration of VZIG to those who are exposed and born to susceptible mothers may be prudent. These infants should be considered at risk for as long as they are hospitalized. Premature infants < 28 weeks’ gestation or who weigh 1000 g or less at birth, who are exposed to VZV, should receive VZIG, regardless of maternal history, because such infants are born before they have acquired adequate maternal antibody transplacentally. Most premature infants of 28 weeks’ gestation or greater born to immune mothers have enough transplacental antibody to protect them from severe disease and complications.

Although infants are at higher risk for serious and fatal complications than older children, the risk for healthy, full-term infants who develop varicella following post-natal exposure is substantially less than for infants whose mothers were infected 5 days before to 2 days after delivery. VZIG is not generally recommended for healthy, full-term neonates or infants who are exposed post-natally, even if their mothers have no history of varicella infection.

Neonates who develop chicken pox despite being given VZIG are at less risk of severe infection than are untreated babies, but can still develop severe infection despite VZIG. For this reason, many authorities recommend treating such babies with intravenous acyclovir.

**Immunocompromised children and VZIG**

Following household exposure, attack rates among immunocompromised children and adolescents given VZIG are 33–50%. Data are not available for immunocompromised, susceptible persons who were not given VZIG. The risk for varicella following close contact (e.g., contact with playmates) or hospital exposure is approximately 20% of the risk occurring from household exposure.

VZIG is recommended for passive immunization of susceptible, immunocompromised children after substantial exposure to varicella or herpes zoster, including
children who (a) have primary and acquired immunodeficiency disorders, (b) have neoplastic diseases, and (c) are receiving immunosuppressive treatment. Immunocompromised children who have a positive past history of varicella (except for bone marrow transplant recipients) can be considered immune. A non-Cochrane meta-analysis suggests that children with acute lymphoblastic leukemia can be expected to mount an adequate immune response, even if they have undetectable antibody, provided they are not too immunosuppressed.\textsuperscript{120}

The CDC recommends that children who receive hematopoietic stem cell transplants should be considered susceptible, regardless of whether they or their donors have a prior history of varicella or varicella vaccination.\textsuperscript{24,107} In contrast, some authorities feel that children with VZV-specific IgG are protected and do not routinely recommend prophylaxis.\textsuperscript{121}

**Post-exposure prophylaxis with acyclovir**

We found three studies on the prophylactic use of acyclovir in susceptible, immunocompetent children following household exposure to varicella.\textsuperscript{122–124} Prophylaxis given in the second week after exposure (7–14 days) was 73–93\% protective against clinical varicella.\textsuperscript{122–124} Prophylaxis in the first week after exposure was less protective against clinical disease. The major disadvantage was that about 15\% of children failed to seroconvert and remained susceptible. On the other hand, the advantage was that acyclovir could be used at a time after exposure when VZV vaccine and immunoglobulin are no longer effective.

There are case reports but no trials of acyclovir prophylaxis for immunocompromised children\textsuperscript{125} and neonates.\textsuperscript{126} Post-exposure use of acyclovir may be an alternative to VZIG in some cases, and is likely to be beneficial for high-risk patients when VZIG is unavailable or if exposure was more than 4 days earlier.

**References**


61 Hiremath GS, Omer SB. A meta-analysis of studies comparing the respiratory route with the subcutaneous route of measles vaccine administration. *Hum Vaccin* 2005;1:30–6.


112 CDC. Varicella zoster immune globulin for the prevention of chickenpox. MMWR 1984;33:84–90, 95–100.
121 Weinstock DM, Boechk M, Boulad F et al. Post-exposure prophylaxis against varicella-zoster virus infection among


APPENDIX 1
Renal impairment and antimicrobials

Renal impairment is mainly important for antimicrobials or their metabolites excreted by the kidneys, e.g., aminoglycosides. These may necessitate dose adjustments in terms of the starting dose or duration of an antimicrobial (see Appendix 2).

A.1.1 Creatinine clearance

Serum creatinine is not an accurate enough measure of renal function and can be normal in renal failure. Creatinine clearance, which provides a measure of glomerular filtration rate (GFR), is preferred. The most accurate measures of creatinine clearance use the excretion of radioactive-labeled tracers, e.g., technetium Tc99m-labeled DTPA scanning. Schwartz and colleagues developed an equation for children based on their serum creatinine and body length.\(^1,2\) The Schwartz equation has been evaluated in comparison to radioactive techniques and is more sensitive than serum creatinine in detecting impaired renal function.\(^3,4\) The Schwartz equation tends to overestimate creatinine clearance, but to a negligible extent when renal function is mildly impaired (GFR 50–90 mL/min). When renal function is moderately impaired (GFR 15–50 mL/min) GFR is overestimated only by about 10%, but by 164% when GFR is <15 mL/min.\(^4\)

The Schwartz equation is inaccurate in critically ill children,\(^5,6\) but is useful in children who are about to undergo hematopoietic stem cell transplantation, being most accurate if they are <5 years old.\(^7\)

The Schwartz equation is sufficiently accurate to provide an estimate of creatinine clearance to make dose adjustments. We recommend the Schwartz equation for estimating creatinine clearance in children unless they are critically ill (see Table A.1.1).

Table A.1.1 Schwartz formula for calculating creatinine clearance in children.

<table>
<thead>
<tr>
<th>Age</th>
<th>Formula for Creatinine Clearance in mL/min/1.73 m(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm neonate</td>
<td>29 × length (cm)/[serum creatinine (mmol/L) × 1000] OR</td>
</tr>
<tr>
<td></td>
<td>0.33 × length (cm)/serum creatinine (mg/100 mL)</td>
</tr>
<tr>
<td>1 month to &lt;1 year</td>
<td>40 × height (cm)/[serum creatinine (mmol/L) × 1000] OR</td>
</tr>
<tr>
<td></td>
<td>0.45 × height (cm)/serum creatinine (mg/100 mL)</td>
</tr>
<tr>
<td>1 year to &lt;12 year</td>
<td>49 × height (cm)/[serum creatinine (mmol/L) × 1000] OR</td>
</tr>
<tr>
<td></td>
<td>0.55 × height (cm)/serum creatinine (mg/100 mL)</td>
</tr>
<tr>
<td>12 years or older (female)</td>
<td>49 × height (cm)/[serum creatinine (mmol/L) × 1000] OR</td>
</tr>
<tr>
<td></td>
<td>0.55 × height (cm)/serum creatinine (mg/100 mL)</td>
</tr>
<tr>
<td>12 years or older (male)</td>
<td>62 × height (cm)/[serum creatinine (mmol/L) × 1000] OR</td>
</tr>
<tr>
<td></td>
<td>0.7 × height (cm)/serum creatinine (mg/100 mL)</td>
</tr>
</tbody>
</table>
A.1.2 Dose or interval adjustment of antimicrobials in renal insufficiency

Antimicrobial therapy can be altered in renal impairment by reducing the dose or by extending the interval between doses. We found two different tables giving recommendations on dose or interval adjustments in children.\(^8\) The recommendations were quite different and neither publication gave the primary data for making the recommendations.\(^8\)\(^9\) One paper said its table was based on pharmaceutical company drug information sheets, PICU dosing guidelines, publications, an electronic database, and extrapolation from adult doses.\(^9\) We are unable to recommend one of these tables in preference to the other because of lack of data, and recommend consulting the product information sheet for dose or interval adjustment when prescribing an antimicrobial for a patient with impaired renal function.

References

A.2.1 Aminoglycosides

Aminoglycosides are antibiotics that are rapidly bactericidal against aerobic Gram-negative bacilli. They also have some activity against *Staphylococcus aureus* and coagulase negative staphylococci, which is potentially useful in neonatal sepsis when aminoglycosides are used with an antistaphylococcal antibiotic. Aminoglycosides are associated with a phenomenon called the post-antibiotic effect where bacteria continue to be killed even after blood levels have fallen below the minimum inhibitory concentration (MIC) of the organism. This is probably because aminoglycosides are still present and active in the intracellular environment where they block protein synthesis at the ribosome but are not detectable in the extracellular space. Killing of bacteria by aminoglycosides is thought to be concentration-dependent, and to depend more on the total amount of antibiotic, the “area under the curve,” in contrast to beta-lactams like penicillin, whose optimal killing depends on maintaining blood levels above the MIC of the organism for as long as possible.1-3

Aminoglycosides accumulate in renal tissue and otolymph,4 and are nephrotoxic and ototoxic. Almost all patients develop some nephrotoxicity with prolonged use of aminoglycosides, even if serum aminoglycoside levels are within the designated therapeutic range.1-3 For this reason, prolonged use should be avoided and aminoglycosides should be stopped within 7 days whenever possible.1-3

There are very few absolute contraindications to aminoglycosides. We recommend that an alternative antibiotic be used if possible, however, or at least that aminoglycoside be stopped within 3 days for children with any of the conditions shown in Table A.2.1, which are known to predispose to aminoglycoside toxicity.1-3,5-7

<table>
<thead>
<tr>
<th>Table A.2.1</th>
<th>Preexisting conditions that predispose to aminoglycoside toxicity.</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Chronic renal failure or deteriorating renal function5</td>
<td></td>
</tr>
<tr>
<td>- Chronic liver disease6</td>
<td></td>
</tr>
<tr>
<td>- Severe cholestasis6</td>
<td></td>
</tr>
<tr>
<td>- Significant conductive hearing problems1-3</td>
<td></td>
</tr>
<tr>
<td>- Vestibular problems (e.g., dizziness, vertigo, or tinnitus)7</td>
<td></td>
</tr>
</tbody>
</table>

We recommend monitoring aminoglycoside levels and renal function regularly, at least every 2–3 days, if patients need to be on aminoglycosides for prolonged periods. We also recommend warning the child and/or parents of the potential risks of aminoglycosides and discussing any possible alternatives. We advise monitoring children on prolonged aminoglycosides clinically for hearing and balance problems, and considering formal vestibular function testing and high-frequency audiometric testing, if available, for older children, e.g., children with endocarditis (see Section 3.1, p. 14).

A.2.2 Starting doses of aminoglycosides

The recommended starting dose depends on the volume of distribution and renal clearance, which are related to body weight and renal function. Aminoglycosides are excreted by the kidneys and so renal function is critical. A guide to calculating creatinine clearance in children is given in Table A.1.1.

Initial doses of aminoglycosides for patients with normal renal function are given in Table A.2.2 and are derived from References 2, 3, and 7. Low-dose aminoglycosides are used for synergy in endocarditis (see Section 3.1, p. 17).
Table A.2.2 Aminoglycoside starting doses for patients with normal renal function.

<table>
<thead>
<tr>
<th>Age</th>
<th>Starting Dose for Gentamicin, Tobramycin</th>
<th>Starting Dose for Amikacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates &lt; 34 weeks</td>
<td>2.5 mg/kg/dose 18–24-hourly</td>
<td>7.5 mg/kg/dose 12–24-hourly</td>
</tr>
<tr>
<td>Neonates ≥34 weeks</td>
<td>2.5–7.5 mg/kg/day</td>
<td>7.5–10 mg/kg/dose 8–12-hourly</td>
</tr>
<tr>
<td>&lt; 10 years</td>
<td>7.5 mg/kg/day</td>
<td>30 mg/kg/day</td>
</tr>
<tr>
<td>10 years and older</td>
<td>6 mg/kg/day</td>
<td>24 mg/kg/day</td>
</tr>
<tr>
<td>Any age: streptococcal</td>
<td>Gentamicin 1 mg/kg/dose, 8-hourly (see</td>
<td>Not recommended</td>
</tr>
<tr>
<td>and enterococcal</td>
<td>Section 3.1</td>
<td></td>
</tr>
<tr>
<td>endocarditis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Some doses are given in mg/kg/dose and then the dose interval, others are given as mg/kg/day which is the total daily dose given once or three times per day.
Adapted from Reference 8, with permission.

For children with impaired renal function, either starting doses should be reduced (see Table A.2.3) or the interval between doses should be increased (see Table A.2.4). Whichever is chosen, aminoglycoside levels and renal function should be monitored very closely.

A.2.3 Dosing interval of aminoglycosides

Question | In neonates and children, is once-daily aminoglycoside compared with multiple-daily dosing safe and effective?

Literature review | We found a non-Cochrane meta-analysis of 16 studies in neonates, a non-Cochrane meta-analysis of 24 studies in children of all ages, and a Cochrane systematic review of 4 studies in children with cystic fibrosis.

Table A.2.3 Reduced aminoglycoside starting doses for patients with impaired renal function.

<table>
<thead>
<tr>
<th>Creatinine Clearance</th>
<th>Starting Dose (% of Usual Recommended Dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mL/s/1.73 m²</td>
<td>mL/min/1.73 m²</td>
</tr>
<tr>
<td>&gt; 1.1</td>
<td>&gt; 66</td>
</tr>
<tr>
<td>0.9–1.1</td>
<td>54–66</td>
</tr>
<tr>
<td>0.7–0.9</td>
<td>42–54</td>
</tr>
<tr>
<td>0.5–0.7</td>
<td>30–42</td>
</tr>
<tr>
<td>0.35–0.5</td>
<td>21–30</td>
</tr>
<tr>
<td>&lt; 0.35</td>
<td>&lt; 21</td>
</tr>
</tbody>
</table>

Use either the method in Table A.2.3 above or the prolonged interval method in Table A.2.4, not both.
Adapted from Reference 8, with permission.

A non-Cochrane meta-analysis in neonates found 16 studies, mostly of good quality, which compared extended interval dosing (once daily or less frequent) with multiple-daily dosing. Extended interval dosing of aminoglycosides in neonates was found to be safe and effective, with no increase in nephrotoxicity or ototoxicity and with a reduced risk of serum drug concentrations outside the therapeutic range.

The non-Cochrane meta-analysis in children of all ages compared once-daily with multiple-daily dosing in different clinical settings: neonatal intensive care unit 6 studies; cystic fibrosis 3 studies; cancer 5 studies; urinary tract infections 4 studies; diverse infectious indications 5 studies; pediatric intensive care unit 1 study. Aminoglycosides used were gentamicin (11 studies), amikacin (9), tobramycin (2), netilmicin (2), and tobramycin or netilmicin (1). There was no significant difference between once-daily and multiple-daily dosing in clinical failure rate, in microbiologic failure rate, and in combined clinical or microbiologic failure rates, but trends favored once-daily dosing consistently. There was no difference in ototoxicity, and no difference in nephrotoxicity as measured by serum creatinine, but urinary excretion of proteins or phospholipids, which were called secondary nephrotoxicity outcomes, significantly favored once-daily dosing.

For children with cystic fibrosis, the Cochrane systematic review found 11 studies, but only 4 eligible RCTs. The efficacy was similar but once-daily dosing was less nephrotoxic than multiple-daily dosing in children (although not in adults).
We found one RCT that showed that once-daily dosing is safe and effective in malnourished children.\textsuperscript{12}

Once-daily dosing has been shown to be as effective as multiple-daily dosing in most clinical settings, and if anything less nephrotoxic. It is also easier to give aminoglycosides once daily in clinical practice.

\textbf{We recommend once-daily (or less frequent) dosing of aminoglycosides in most clinical settings.}

We do not recommend once-daily dosing for children in situations where unconventional kinetics are likely (e.g., patients with burns and others with large volumes of distribution). In addition, there is insufficient evidence currently to say whether once-daily dosing is preferred to multiple-daily dosing for the treatment of endocarditis.

\section*{A.2.4 Monitoring plasma levels of aminoglycosides}

It is recommended to monitor plasma levels for all patients in whom it is anticipated that aminoglycosides will be given for more than 48 hours. Neonates are often started on empiric therapy with a beta-lactam and an aminoglycoside, but only about 10% have bacteremia and need to continue antibiotics beyond 48–72 hours. It is necessary to measure levels only for babies who continue aminoglycosides unless they have renal problems.

\textbf{Once-daily or less frequent dosing}

For once-daily or less frequent dosing of aminoglycosides, the reasons for measuring aminoglycosides may be to measure total therapeutic dose, in which case an area-under-the-curve method is appropriate, or to detect accumulation, in which case a trough level would be needed.

\textbf{Area-under-the-curve methods}

The most accurate way to measure the “area under the curve” (i.e., to estimate the total amount of aminoglycoside in the plasma between doses) is to measure the plasma aminoglycoside level twice, once about an hour after the dose was given that will be near the peak, and another after 6–14 hours. The 24-hour area under the curve (AUC) can then be calculated using a computer program, which also recommends the appropriate dose or interval adjustment. When computer-based methods are not available, graphical methods can be used instead.\textsuperscript{4,8,13–15} An example of a nomogram is given in Figure A.2.1 and the calculation in Table A.2.5. Nomograms have been studied mainly in adults. The advantage is that they need only a single measurement and are easy to calculate, but somewhat less accurate. The nomogram recommended in \textit{Therapeutic Guidelines}\textsuperscript{4} (see Figure A.2.1) has been compared with a manual method and two computer programs.\textsuperscript{16} The \textit{Therapeutic Guidelines} nomogram works well for patients with normal or mildly impaired renal function (creatinine clearance [CrCl] 60–90 mL/min/1.73 m\textsuperscript{2}). For patients with moderate renal impairment (CrCl 30–60), the nomogram estimates lower doses than the computer programs.\textsuperscript{16}

For once-daily dosing of gentamicin or tobramycin, up to 7 mg/kg/day, a single measurement of plasma concentration should be made between 6 and 14 hours.
after the end of the infusion. When using the dose adjustment method, the plasma concentration is compared to the graph in Figure A.2.1.

If the plotted plasma concentration is between the maximum and minimum lines on the graph, no dose adjustment is needed. If the plasma concentration is above the maximum line or below the minimum line, a proportional decrease or increase in dose is recommended (see Table A.2.5).

The level should be measured after the first dose and the dose adjusted if necessary. It should be repeated daily if the clinical state, especially renal function, is unstable and otherwise every 3–5 days.

Table A.2.5 Calculating dose adjustment from nomogram.

<table>
<thead>
<tr>
<th>Dose of aminoglycoside*</th>
<th>= 5 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual concentration at 9 hours</td>
<td>= 5.4 mg/L</td>
</tr>
<tr>
<td>Target concentration, calculated from the midpoint of the two lines</td>
<td>= 2.7 mg/L</td>
</tr>
</tbody>
</table>

Next dose = Target concentration/actual concentration × initial dose = 2.7/5.4 × 5 mg/kg = 2.5 mg/kg

*This method of dose adjustment applies to gentamicin, netilmicin, and tobramycin. For once-daily amikacin dosing, divide the measured actual concentration by 4 and use the same graph. From Reference 8, with permission.

An alternative method that involves altering the dosing interval according to a nomogram instead of altering the dose of aminoglycoside has not been evaluated and we cannot recommend it.

Trough measurements for once-daily dosing
The recommended trough levels when using once-daily dosing are <1 mg/L for gentamicin or tobramycin and <5 mg/L for amikacin.

Multiple-daily dosing
The commonest method for monitoring multiple-daily dosing (usually 8- or 12-hourly doses) of aminoglycosides is by measuring peak and trough plasma levels.

Trough levels, taken just before the next dose is due, are measured to prevent drug accumulation and reduce risk of toxicity. They should be repeated at least every 3–5 days and more frequently if there is impaired renal function.

Peak levels are measured to ensure that the dose of aminoglycoside is adequate. Blood is collected 30 minutes after completion of the infusion of a dose of aminoglycoside.

The usual recommended target trough and peak levels are in Table A.2.6. It is not appropriate to apply these peak and trough levels to once-daily dosing.

For monitoring 8-hourly low-dose (1 mg/kg) gentamicin use in endocarditis, we recommend...
Table A.2.6  Recommended aminoglycoside trough and peak levels for multiple-daily dosing.

<table>
<thead>
<tr>
<th>Aminoglycoside</th>
<th>Recommended Trough level (mg/L)</th>
<th>Recommended Peak Level (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>&lt; 10</td>
<td>20–30</td>
</tr>
<tr>
<td>Gentamicin and tobramycin</td>
<td>&lt; 2</td>
<td>5–10</td>
</tr>
<tr>
<td>Gentamicin in endocarditis</td>
<td>&lt; 1</td>
<td>None recommended</td>
</tr>
</tbody>
</table>

performing trough levels and keeping the level <1 mg/L to avoid toxicity.

References

## APPENDIX 3

### Antimicrobial drug dose recommendations

**Table A.3.1** Antimicrobial drug dose recommendations

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Indication(s)</th>
<th>Dose (Do Not Exceed Adult Dose)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>Usual dose, e.g., herpes simplex labialis (cold sores), herpetic whitlow</td>
<td>5–10 mg/kg (max 400 mg) orally, 5 times daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eczema herpeticum, herpes simplex virus (HSV) encephalitis (except neonatal), ophthalmic herpes zoster, severe mucocutaneous HSV infections, severe varicella</td>
<td>10 mg/kg (max 400 mg) IV, 8-hourly or 1.5 g/m²/day in three divided doses</td>
<td>Monitor renal function</td>
</tr>
<tr>
<td></td>
<td>Neonatal HSV infection, including disseminated disease, encephalitis, hepatitis, pneumonitis, skin lesions</td>
<td>20 mg/kg IV, 8-hourly (14 days for localized disease, 21 days for encephalitis or disseminated disease)</td>
<td>Monitor renal function</td>
</tr>
<tr>
<td>Albendazole (6 months or older)</td>
<td>Community worm programs, hookworm, roundworm, threadworm</td>
<td>≤10 kg: 200 mg, &gt;10 kg: 400 mg orally, as a single dose</td>
<td>Only recommended for children &gt;6 months old</td>
</tr>
<tr>
<td></td>
<td>Cutaneous larva migrans, strongyloidiasis, whipworm</td>
<td>≤10 kg: 200 mg, &gt;10 kg: 400 mg orally, daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Microsporidiosis</td>
<td>≤10 kg: 200 mg, &gt;10 kg: 400 mg orally, 12-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hydatid disease</td>
<td>&gt;6 years: 7.5 mg/kg (max 400 mg) 12-hourly, orally</td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>Term neonates ≤7 days</td>
<td>15 mg/kg IV, daily OR 7.5 mg/kg IV, 12-hourly</td>
<td>See Appendix 2 for preterm neonates</td>
</tr>
<tr>
<td></td>
<td>Term neonates &gt; 7 days</td>
<td>22.5 mg/kg IV, daily OR 7.5 mg/kg IV, 8-hourly</td>
<td>See Appendix 2 for preterm neonates</td>
</tr>
<tr>
<td></td>
<td>Single daily dose</td>
<td>24 mg/kg (max 1 g) IV, daily</td>
<td>Single daily dosing regimen not recommended for patients with renal impairment or cancer monitor drug levels: for once-daily dosing, take level at 6–14 hours and use nomogram (Appendix 2); or trough &lt; 5 mg/L</td>
</tr>
<tr>
<td></td>
<td>Three times a day</td>
<td>7.5 mg/kg (max 300 mg) IV, 8-hourly</td>
<td>Monitor levels: aim for trough: &lt;10 mg/L peak: 20–30 mg/L</td>
</tr>
</tbody>
</table>
### Table A.3.1 (Continued)

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Indication(s)</th>
<th>Dose (Do Not Exceed Adult Dose)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>Usual dose</td>
<td>15 mg/kg (max 500 mg) orally, 8-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cholera</td>
<td>10 mg/kg (max 250 mg) orally, 6-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Community-acquired pneumonia</td>
<td>25 mg/kg (max 1 g) orally, 8-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gonococcal conjunctivitis</td>
<td>75 mg/kg (max 3 g) orally, as a single dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Typhoid and paratyphoid fevers</td>
<td>25 mg/kg (max 1 g) orally, 6-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pyelonephritis</td>
<td>25 mg/kg (max 1 g) IV, 6-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe sepsis</td>
<td>50 mg/kg (max 2 g) IV, 6-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enterococcal endocarditis, meningitis</td>
<td>50 mg/kg (max 2 g) IV, 4-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endocarditis prophylaxis</td>
<td>50 mg/kg (max 2 g) orally or IV, as a single dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post-splenectomy prophylaxis</td>
<td>&lt;2 years: 20 mg/kg, ≥2 years: 250 mg orally, daily</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin + clavulanate</td>
<td>Usual dose</td>
<td>22.5 + 3.2 mg/kg (max 875 + 125 mg) orally, 12-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe infection, e.g., bacterial sinusitis, pneumonia</td>
<td>22.5 + 3.2 mg/kg (max 875 + 125 mg) orally, 8-hourly</td>
<td></td>
</tr>
<tr>
<td>Amphotericin B desoxycholate (conventional)</td>
<td>Candidal sepsis, fungal pneumonia</td>
<td>1 mg/kg IV, daily</td>
<td>Use instead of conventional amphotericin B if preexisting renal impairment, nephrotoxicity, or severe infusion-related toxicity (dose 1 mg/kg) (see p. 123)</td>
</tr>
<tr>
<td>Amphotericin (liposomal)</td>
<td>Systemic aspergillosis, systemic candidiasis, mould infections (Fusarium, Zygomycetes)</td>
<td>3 mg/kg IV, daily for candidiasis, 3–5 mg/kg IV, daily for aspergillosis, 5 mg/kg IV, daily for mould infections</td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Usual dose</td>
<td>25 mg/kg (max 1 g) IV, 6-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pyelonephritis</td>
<td>25 mg/kg (max 1 g) IV, 6-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe sepsis</td>
<td>50 mg/kg (max 2 g) IV, 6-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enterococcal endocarditis, meningitis</td>
<td>50 mg/kg (max 2 g) IV, 4-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endocarditis prophylaxis</td>
<td>50 mg/kg (max 2 g) IV, as a single dose</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Indication(s)</th>
<th>Dose (Do Not Exceed Adult Dose)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin-sulbactam</td>
<td>Usual dose</td>
<td>30 mg/kg (max 2 g) of ampicillin IV, 6-hourly</td>
<td>Not licensed for infants and children</td>
</tr>
<tr>
<td></td>
<td>Severe infection</td>
<td>50–100 mg/kg (max 4 g) of ampicillin IV, 6-hourly</td>
<td></td>
</tr>
<tr>
<td>Atovaquone+proguanil</td>
<td>Uncomplicated <em>Plasmodium falciparum</em> malaria</td>
<td>11–20 kg: 1 tablet, 21–30 kg: 2 tablets, 31–40 kg: 3 tablets, &gt; 40 kg: 4 tablets orally, daily (atovaquone+proguanil 250 + 100 mg strength)</td>
<td>Only recommended for children &gt; 10 kg</td>
</tr>
<tr>
<td>Azithromycin</td>
<td><em>Mycobacterium avium</em> complex</td>
<td>15 mg/kg (max 600 mg) orally, daily</td>
<td>Only recommended for children &gt; 6 kg</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>10 mg/kg orally, daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Chlamydia trachomatis</em> conjunctivitis, post-sexual assault prophylaxis, gonorrhea, chlamydia</td>
<td>20 mg/kg (max 1 g) orally, as a single dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Salmonella or shigella enteritis</td>
<td>20 mg/kg (max 1 g) orally on the first day, followed by 10 mg/kg (max 500 mg) orally, daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Typhoid</td>
<td>20 mg/kg orally or IV, daily for 5 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pertussis, cat scratch disease</td>
<td>10 mg/kg (max 500 mg) orally on day 1, then 5 mg/kg orally, daily for 4 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Early syphilis</td>
<td>50 mg/kg (max 2 g) orally, as a single dose</td>
<td></td>
</tr>
<tr>
<td>Aztreonam</td>
<td>Usual dose</td>
<td>30 mg/kg (max 1.2 g) IV, 6–8-hourly</td>
<td>Modify dose in renal failure</td>
</tr>
<tr>
<td></td>
<td>Severe infection</td>
<td>50 mg/kg (max 2 g) IV, 6–8-hourly</td>
<td></td>
</tr>
<tr>
<td>Benzathine penicillin</td>
<td>Rheumatic fever prophylaxis</td>
<td>900 mg (1.5 million U) IM, every 3–4 weeks</td>
<td>Mix 2 mL in syringe with 0.5-mL lignocaine</td>
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<tr>
<td></td>
<td>Early syphilis</td>
<td>30 mg (50,000 U)/kg (max 1.2 g or 2 million U) IM, as a single dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Late latent syphilis</td>
<td>30 mg (50,000 U)/kg (max 1.2 g or 2 million U) IM, once weekly</td>
<td>For three doses</td>
</tr>
<tr>
<td>Benzylpenicillin</td>
<td>Usual dose</td>
<td>30 mg (50,000 U)/kg (max 1.2 g or 2 million U) IV, 4–6-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe infection, e.g., meningitis, endocarditis, necrotizing fasciitis, tertiary syphilis</td>
<td>60 mg (100,000 U)/kg (max 2.4 g or 4 million U) IV, 4-hourly</td>
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</table>
### Table A.3.1 (Continued)

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Indication(s)</th>
<th>Dose (Do Not Exceed Adult Dose)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefaclor</td>
<td>Otitis media</td>
<td>10 mg/kg (max 250 mg) orally, 8-hourly</td>
<td>Second or third line choice</td>
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<tr>
<td>Cefadroxil</td>
<td>Otitis media</td>
<td>15 mg/kg (max 600 mg) orally, 12-hourly</td>
<td></td>
</tr>
<tr>
<td>Cefazolin</td>
<td>Usual dose</td>
<td>15 mg/kg (max 600 mg) IV, 8-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Serious staphylococcal infections</td>
<td>25 mg/kg (max 1 g) IV, 8-hourly</td>
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<tr>
<td>Cefdinir</td>
<td>Streptococcal sore throat</td>
<td>7 mg/kg (max 300 mg) orally, 12-hourly</td>
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<tr>
<td>Cefixime</td>
<td>Urinary tract infection</td>
<td>4 mg/kg (max 160 mg) orally, 12-hourly</td>
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<tr>
<td></td>
<td>Gonorrhea</td>
<td>20 mg/kg (max 800 mg) orally, as a single dose</td>
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</tr>
<tr>
<td>Cefepime</td>
<td>Hospital-acquired pneumonia, <em>Pseudomonas sepsis</em>, febrile neutropenia</td>
<td>50 mg/kg (max 2 g) IV, 8-hourly</td>
<td>Modify dose in renal failure</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>Usual dose</td>
<td>25 mg/kg (max 1 g) IV, 6–8-hourly</td>
<td>Cefotaxime has no useful activity against <em>Pseudomonas</em> modify dose in renal failure</td>
</tr>
<tr>
<td></td>
<td>Severe infection, e.g., brain abscess, meningitis</td>
<td>50–75 mg/kg (max 3 g) IV, 6-hourly</td>
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<tr>
<td></td>
<td>Gonorrhea</td>
<td>25 mg/kg (max 1 g) IM, as a single dose</td>
<td></td>
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<tr>
<td>Cefotetan</td>
<td>Severe infections, pelvic inflammatory disease</td>
<td>40 mg/kg (max 2 g) IV, 12-hourly</td>
<td>Modify dose in renal failure</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>Severe infections</td>
<td>40 mg/kg (max 2 g) IV, 6-hourly</td>
<td>Modify dose in renal failure</td>
</tr>
<tr>
<td>Cefpirome</td>
<td><em>Pseudomonas sepsis</em></td>
<td>50 mg/kg (max 2 g) IV, 12-hourly</td>
<td>Modify dose in renal failure</td>
</tr>
<tr>
<td>Cefpodoxime proxetil</td>
<td>Usual dose, e.g., streptococcal sore throat, pneumonia, urinary tract infection</td>
<td>5 mg/kg (max 200 mg) orally, 12-hourly</td>
<td>Modify dose in renal failure</td>
</tr>
<tr>
<td></td>
<td>More severe infection</td>
<td>8 mg/kg (max 320 mg) orally, 12-hourly</td>
<td></td>
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<tr>
<td>Cefprozil</td>
<td>Otitis media</td>
<td>15 mg/kg (max 600 mg) orally, 12-hourly</td>
<td>Modify dose in renal failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Antimicrobial</td>
<td>Indication(s)</td>
<td>Dose (Do Not Exceed Adult Dose)</td>
<td>Notes</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------------------------</td>
<td>---------------------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>Febrile neutropenia, <em>Pseudomonas sepsis</em></td>
<td>50 mg/kg (max 2 g) IV, 8-hourly</td>
<td>Modify dose in renal failure</td>
</tr>
<tr>
<td></td>
<td>Melioidosis</td>
<td>50 mg/kg (max 2 g) IV, 6-hourly</td>
<td>Modify dose in renal failure</td>
</tr>
<tr>
<td>Ceftibuten</td>
<td>Otitis media</td>
<td>9 mg/kg (max 400 mg) orally, daily</td>
<td>Modify dose in renal failure</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Usual dose</td>
<td>50 mg/kg (max 2 g) IV, daily</td>
<td>Not recommended in neonates: displaces bilirubin from albumin</td>
</tr>
<tr>
<td></td>
<td>Severe infection, e.g., brain abscess, meningitis</td>
<td>50 mg/kg (max 2 g) IV, 12-hourly OR 100 mg/kg (max 4 g) IV, daily</td>
<td></td>
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<tr>
<td></td>
<td>Endophthalmitis, presumed meningococcal infection</td>
<td>50 mg/kg (max 2 g) IV, as a single dose</td>
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<tr>
<td></td>
<td><em>Haemophilus influenzae</em> type b meningitis prophylaxis</td>
<td>50 mg/kg (max 2 g) IM, daily for 4 days</td>
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<tr>
<td></td>
<td>Typhoid and paratyphoid fevers</td>
<td>75 mg/kg (max 3 g) IV, daily</td>
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<tr>
<td></td>
<td><em>Neisseria gonorrhoeae</em> infection</td>
<td>≤45 kg: 125 mg, &gt; 45 kg: 250 mg IM, as a single dose</td>
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<tr>
<td></td>
<td><em>N. meningitidis</em> meningitis prophylaxis</td>
<td>125 mg IM, as a single dose</td>
<td></td>
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<tr>
<td>Cefuroxime</td>
<td>Otitis media, sinusitis</td>
<td>10–15 mg/kg (max 500 mg) orally, 12-hourly</td>
<td>Modify dose in renal failure</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>Usual dose</td>
<td>25 mg/kg (max 1 g) orally, 8-hourly</td>
<td>Modify dose in renal failure</td>
</tr>
<tr>
<td></td>
<td>Epididymoorchitis, cystitis</td>
<td>12.5 mg/kg (max 500 mg) orally, 12-hourly</td>
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<tr>
<td></td>
<td>Recurrent urinary tract infection prophylaxis</td>
<td>12.5 mg/kg (max 500 mg) orally, nightly</td>
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<tr>
<td></td>
<td>Endocarditis prophylaxis</td>
<td>50 mg/kg (max 2 g) orally, as a single dose</td>
<td>As an alternative if allergic to amoxicillin</td>
</tr>
<tr>
<td>Cephalothin</td>
<td>Usual dose</td>
<td>25 mg/kg (max 1 g) IV, 6-hourly</td>
<td>Modify dose in renal failure</td>
</tr>
<tr>
<td></td>
<td>Severe infection</td>
<td>50 mg/kg (max 2 g) IV, 6-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surgical prophylaxis</td>
<td>50 mg/kg (max 2 g) IV, as a single dose</td>
<td></td>
</tr>
<tr>
<td>Cephazolin</td>
<td>Usual dose</td>
<td>25 mg/kg (max 1 g) IV, 6-hourly</td>
<td>Modify dose in renal failure</td>
</tr>
<tr>
<td></td>
<td>Severe sepsis</td>
<td>50 mg/kg (max 1 g) IV, 8-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surgical prophylaxis</td>
<td>25 mg/kg (max 1 g) IV, as a single dose</td>
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</table>
Table A.3.1  (Continued)

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Indication(s)</th>
<th>Dose (Do Not Exceed Adult Dose)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephradine</td>
<td>Usual dose</td>
<td>25 mg/kg (max 1 g) orally, 12-hourly</td>
<td>Modify dose in renal failure</td>
</tr>
<tr>
<td></td>
<td>Severe infection</td>
<td>25 mg/kg (max 1 g) IV, 6-hourly</td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Rickettsial infections</td>
<td>12.5 mg/kg (max 500 mg) orally/IV, 6-hourly</td>
<td>Because of risk of aplastic anemia use only if no better alternative</td>
</tr>
<tr>
<td></td>
<td>Typhoid and paratyphoid fevers</td>
<td>25 mg/kg (max 750 mg) orally or IV, 6-hourly</td>
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</tr>
<tr>
<td>Chloroquine</td>
<td>Malaria prophylaxis</td>
<td>5 mg base/kg orally, weekly</td>
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</tr>
<tr>
<td></td>
<td><em>Plasmodium vivax, P. malariae, and P. ovale malaria</em></td>
<td>10 mg base/kg orally, then 5 mg base/kg 6 hourly later and on days 2 and 3</td>
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</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Usual dose</td>
<td>10 mg/kg (max 500 mg) orally, 12-hourly</td>
<td>Caution family about possible risk of Achilles tendonitis</td>
</tr>
<tr>
<td></td>
<td>Severe infection, e.g., <em>Pseudomonas sepsis</em></td>
<td>15 mg/kg (max 600 mg) IV or orally, 12-hourly</td>
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<tr>
<td></td>
<td>Cholera</td>
<td>25 mg/kg (max 1 g) orally, as a single dose</td>
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</tr>
<tr>
<td></td>
<td>Endophthalmitis, penetrating eye injuries</td>
<td>15 mg/kg (max 750 mg) orally, as a single dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Typhoid and paratyphoid fevers</td>
<td>15 mg/kg (max 500 mg) orally, 12-hourly OR 10 mg/kg (max 400 mg) IV, 12-hourly</td>
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<tr>
<td>Clarithromycin</td>
<td>Cervical lymphadenitis, <em>Mycobacterium avium complex infection, M. marinum infection</em></td>
<td>12.5 mg/kg (max 500 mg) orally, 12-hourly</td>
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<tr>
<td></td>
<td>Pertussis</td>
<td>7.5 mg/kg (max 300 mg) orally, 12-hourly</td>
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<tr>
<td>Clindamycin</td>
<td>Usual dose</td>
<td>10 mg/kg (max 450 mg) IV 8-hourly, then same dose orally 8-hourly</td>
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</tr>
<tr>
<td></td>
<td>Severe infection</td>
<td>15 mg/kg (max 600 mg) IV, 8-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endocarditis prophylaxis</td>
<td>15 mg/kg (max 600 mg) orally/IV, as a single dose</td>
<td></td>
</tr>
<tr>
<td>Cloxacillin</td>
<td>Usual dose</td>
<td>25 mg/kg (max 1 g) orally, 6-hourly</td>
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<tr>
<td>Co-trimoxazole</td>
<td>See trimethoprim-sulfamethoxazole</td>
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<td></td>
</tr>
<tr>
<td>Antimicrobial</td>
<td>Indication(s)</td>
<td>Dose (Do Not Exceed Adult Dose)</td>
<td>Notes</td>
</tr>
<tr>
<td>---------------------</td>
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<td>--------------------------------------------</td>
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<tr>
<td>Dapsone</td>
<td><strong>Pneumocystis jiroveci pneumonia (PCP) treatment</strong></td>
<td>2 mg/kg (max 100 mg) orally, daily</td>
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<tr>
<td></td>
<td>PCP prophylaxis</td>
<td>2 mg/kg (max 100 mg) orally, daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>OR 4 mg/kg (max 200 mg) orally, weekly</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dicloxacillin</td>
<td>Usual dose</td>
<td>12.5 mg/kg (max 500 mg) orally, 6-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate infection</td>
<td>25 mg/kg (max 1 g) orally, 6-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe infection</td>
<td>50 mg/kg (max 2 g) IV, 6-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endocarditis</td>
<td>50 mg/kg (max 2 g) IV, 4-hourly</td>
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</tr>
<tr>
<td></td>
<td>Surgical prophylaxis</td>
<td>50 mg/kg (max 2 g) IV, as a single dose</td>
<td></td>
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<tr>
<td>Diloxanide furoate</td>
<td>Amebiasis</td>
<td>7 mg/kg (max 500 mg) orally, 8-hourly</td>
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<tr>
<td>Doxycycline (9 years or older)</td>
<td>Usual dose</td>
<td>2.5 mg/kg (max 100 mg) orally, 12-hourly</td>
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<tr>
<td></td>
<td>Malaria prophylaxis</td>
<td>2.5 mg/kg (max 100 mg) orally, daily</td>
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<tr>
<td></td>
<td>Bacterial sinusitis</td>
<td>4 mg/kg (max 200 mg) orally, as a single dose, then 2 mg/kg (max 100 mg) orally, daily</td>
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<tr>
<td>Erythromycin (doses are expressed in terms of erythromycin base. For products containing erythromycin ethyl succinate, multiply the dose by 1.6)</td>
<td><strong>Chlamydia trachomatis conjunctivitis, pneumonia</strong></td>
<td>10 mg/kg orally, 6-hourly</td>
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<td></td>
<td>Campylobacter enteritis, pertussis</td>
<td>10 mg/kg (max 500 mg) orally, 6-hourly</td>
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<tr>
<td></td>
<td>Impetigo, cat scratch disease</td>
<td>10 mg/kg (max 500 mg) orally, 12-hourly</td>
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<tr>
<td></td>
<td>Severe infection, e.g., pneumonia</td>
<td>10 mg/kg (max 500 mg) IV, 6-hourly</td>
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<td></td>
<td>Post-splenectomy prophylaxis</td>
<td>250 mg orally, daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Recurrent rheumatic fever prevention</td>
<td>250 mg orally, 12-hourly</td>
<td>Use only if allergic to penicillin</td>
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<tr>
<td>Antimicrobial</td>
<td>Indication(s)</td>
<td>Dose (Do Not Exceed Adult Dose)</td>
<td>Notes</td>
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<tr>
<td>--------------</td>
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<tr>
<td>Ethambutol (6 years or older)</td>
<td>Tuberculosis</td>
<td>15 mg/kg orally, daily OR 30 mg/kg orally, three times a week</td>
<td>&gt; 6 years old only, and check vision</td>
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<td></td>
<td><em>Mycobacterium kansasii</em></td>
<td>25 mg/kg orally, daily</td>
<td></td>
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<tr>
<td></td>
<td><em>M. avium complex infection</em></td>
<td>25 mg/kg orally, daily for 2 months, then 15 mg/kg daily</td>
<td></td>
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<tr>
<td></td>
<td><em>M. marinum infection</em></td>
<td>15 mg/kg orally, daily</td>
<td></td>
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<tr>
<td>Flucloxacillin</td>
<td>Usual dose</td>
<td>12.5 mg/kg (max 500 mg) orally, 6-hourly</td>
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<tr>
<td></td>
<td>Moderate infection</td>
<td>25 mg/kg (max 1 g) orally, 6-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe infection</td>
<td>50 mg/kg (max 2 g) IV, 6-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endocarditis</td>
<td>50 mg/kg (max 2 g) IV, 4-hourly</td>
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<tr>
<td></td>
<td>Surgical prophylaxis</td>
<td>50 mg/kg (max 2 g) IV, as a single dose</td>
<td></td>
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<tr>
<td>Fluconazole</td>
<td>Usual dose, e.g., oral candidiasis</td>
<td>4 mg/kg (max 150 mg) orally, daily</td>
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<td></td>
<td>Mucocutaneous candidiasis</td>
<td>6 mg/kg (max 300 mg) orally, daily</td>
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<td>Candida sepsis</td>
<td>6 mg/kg (max 300 mg) IV daily, then same dose orally</td>
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<tr>
<td></td>
<td>Cryptococcal pneumonia or meningitis</td>
<td>12 mg/kg (max 800 mg) orally or IV for one dose, then 6 mg/kg (max 400 mg) orally, daily</td>
<td></td>
</tr>
<tr>
<td>Flucytosine</td>
<td>Cryptococcal pneumonia or meningitis</td>
<td>25 mg/kg IV or orally, 6-hourly</td>
<td>Modify dose in renal failure</td>
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<tr>
<td>Foscarnet</td>
<td>CMV retinitis, colitis, or esophagitis</td>
<td>60 mg/kg IV, 8-hourly or continuous infusion</td>
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<tr>
<td></td>
<td>Acyclovir-resistant HSV infection</td>
<td>60 mg/kg IV, 12-hourly</td>
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<tr>
<td>Fusidate sodium or fusidic acid suspension</td>
<td>MRSA osteomyelitis or septic arthritis, recurrent staphylococcal skin infection</td>
<td>12 mg/kg (max 500 mg) orally or IV, 12-hourly fusidic acid suspension 18 mg/kg (max 750 mg) orally, 12-hourly (fusidate sodium 500 mg is equivalent to fusidic acid suspension 750 mg)</td>
<td>Not recommended as sole antibiotic, because of rapid emergence of resistance monitor blood levels and adjust dose</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>Cytomegalovirus colitis, retinitis, or esophagitis</td>
<td>5 mg/kg IV, 12-hourly</td>
<td></td>
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</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Indication(s)</th>
<th>Dose (Do Not Exceed Adult Dose)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin</td>
<td>Term neonates ≤ 7 days</td>
<td>5 mg/kg IV, daily OR 2.5 mg/kg IV, 12-hourly</td>
<td>See Appendix 2 for preterm neonates</td>
</tr>
<tr>
<td></td>
<td>Term neonates &gt; 7 days</td>
<td>7.5 mg/kg IV, daily OR 2.5 mg/kg IV, 8-hourly</td>
<td>See Appendix 2 for preterm neonates</td>
</tr>
<tr>
<td></td>
<td>Usual dose</td>
<td>&lt;10 years: 7.5 mg/kg IV daily, 10 years or older: 6 mg/kg IV daily (daily regimen) or 2.5 mg/kg IV 8-hourly (8-hourly regimen)</td>
<td>Modify dose in renal failure single daily dosing regimen not recommended for patients with renal impairment or cancer monitor drug levels: for once-daily dosing, take level at 6–14 hourly and use nomogram (Appendix 2); or trough &lt; 1 mg/L for 8-hourly dosing: aim for peak 5–10 mg/L and trough &lt; 2 mg/L</td>
</tr>
<tr>
<td></td>
<td>Cystic fibrosis</td>
<td>2.5–4 mg/kg (max 80 mg) IV, 8-hourly</td>
<td>Higher doses because of abnormal metabolism</td>
</tr>
<tr>
<td></td>
<td>Brucellosis (&lt; 8 years)</td>
<td>2.5 mg/kg IV, 8-hourly</td>
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<tr>
<td></td>
<td>Endocarditis treatment</td>
<td>1 mg/kg IV, 8-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endocarditis prophylaxis</td>
<td>2.5 mg/kg IV, as a single dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endophthalmitis, penetrating eye injuries</td>
<td>5 mg/kg IV, as a single dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surgical prophylaxis</td>
<td>2 mg/kg IV, as a single dose</td>
<td></td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>Fungal infections</td>
<td>Ultramicrosize 10 mg/kg (max 750 mg) orally, daily microsize: 10 mg/kg (max 500 mg) orally, 12-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Acinetobacter baumanii</em> pneumonia, melioidosis</td>
<td>25 mg/kg (max 1 g) IV, 6-hourly (dose does not include the cilastatin component)</td>
<td>May cause seizures in meningitis or predisposed children</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Tuberculosis</td>
<td>10 mg/kg (max 300 mg) orally daily OR 15 mg/kg (max 600 mg) orally, three times a week</td>
<td></td>
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<tr>
<td></td>
<td><em>Mycobacterium kansasii</em>, tuberculosis chemoprophylaxis</td>
<td>10 mg/kg (max 300 mg) orally daily</td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Usual dose</td>
<td>2.5–5 mg/kg (max 200 mg) orally, 12-hourly</td>
<td>Improved absorption if taken with acid drink, e.g., coca cola</td>
</tr>
<tr>
<td></td>
<td>Pulmonary aspergillosis</td>
<td>7.5 mg/kg (max 300 mg) orally as the capsule, 12-hourly for 3 days, then 5 mg/kg (max 200 mg) orally, 12-hourly</td>
<td></td>
</tr>
<tr>
<td>Antimicrobial</td>
<td>Indication(s)</td>
<td>Dose (Do Not Exceed Adult Dose)</td>
<td>Notes</td>
</tr>
<tr>
<td>-----------------------</td>
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</tr>
<tr>
<td>Ivermectin (&gt;5 years)</td>
<td>Crusted (Norwegian) scabies, cutaneous larva migrans</td>
<td>200 μg/kg orally, as a single dose</td>
<td></td>
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<tr>
<td>Lamivudine</td>
<td>HIV, post-needlestick injury, HIV prophylaxis</td>
<td>4 mg/kg (max 150 mg) orally, 12-hourly</td>
<td>See Chapter 8</td>
</tr>
<tr>
<td></td>
<td>Chronic hepatitis B</td>
<td>3 mg/kg (max 100 mg) orally, daily</td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td>Resistant staphylococcal and enterococcal infections</td>
<td>10 mg/kg (max 400 mg) orally or IV, 8-hourly</td>
<td>May cause myelosuppression</td>
</tr>
<tr>
<td>Liposomal amphotericin</td>
<td>See amphotericin (liposomal)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loracarbef</td>
<td>Otitis media</td>
<td>15 mg/kg (max 600 mg) orally, 12-hourly</td>
<td></td>
</tr>
<tr>
<td>Mebendazole</td>
<td>Threadworm</td>
<td>Up to 10 kg: 50 mg; &gt; 10 kg: 100 mg, orally, as a single dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hookworm, roundworm, whipworm</td>
<td>Up to 10 kg: 50 mg, &gt; 10 kg: 100 mg orally, 12-hourly</td>
<td></td>
</tr>
<tr>
<td>Mefloquine</td>
<td>Uncomplicated Plasmodium falciparum malaria</td>
<td>15 mg/kg (max 750 mg) orally, then 10 mg/kg (max 500 mg) 6–8 hourly later, both as single doses</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Malaria prophylaxis</td>
<td>15–19 kg: 1/4 tablet, 20–30 kg: 1/2 tablet, 31–40 kg: 3/4 tablet orally, weekly (mefloquine 250-mg tablets)</td>
<td></td>
</tr>
<tr>
<td>Meropenem</td>
<td>Acinetobacter baumanii pneumonia, melioidosis</td>
<td>25 mg/kg (max 1 g) IV, 8-hourly</td>
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<tr>
<td></td>
<td>Hospital-acquired meningitis</td>
<td>40 mg/kg (max 2 g) IV, 8-hourly</td>
<td></td>
</tr>
<tr>
<td>Methicillin</td>
<td>Usual dose</td>
<td>25 mg/kg (max 1 g) orally, 6-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate infection</td>
<td>40 mg/kg (max 1.6 g) orally, 6-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe infection</td>
<td>50 mg/kg (max 2 g) IV, 6-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endocarditis</td>
<td>50 mg/kg (max 2 g) IV, 4-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surgical prophylaxis</td>
<td>50 mg/kg (max 2 g) IV, as a single dose</td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Usual dose</td>
<td>10 mg/kg (max 400 mg) orally, 12-hourly</td>
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<tr>
<td></td>
<td>Severe sepsis</td>
<td>12.5 mg/kg (max 500 mg) IV, 8–12-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antibiotic-associated diarrhea, Dientamoeba fragilis diarrhea, giardiasis (see also single daily dose regimen below)</td>
<td>10 mg/kg (max 400 mg) orally, 8-hourly</td>
<td></td>
</tr>
<tr>
<td>Antimicrobial</td>
<td>Indication(s)</td>
<td>Dose (Do Not Exceed Adult Dose)</td>
<td>Notes</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------------------------------------------------</td>
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<tr>
<td>Giardiasis (single daily dose regimen)</td>
<td>30 mg/kg (max 2 g) orally, daily</td>
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<tr>
<td>Amebiasis</td>
<td>15 mg/kg (max 600 mg) orally, 8-hourly</td>
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<tr>
<td>Post-sexual assault prophylaxis</td>
<td>50 mg/kg (max 2 g) orally, as a single dose</td>
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<tr>
<td>Surgical prophylaxis</td>
<td>12.5 mg/kg (max 500 mg) IV, as a single dose</td>
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<td></td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>Pneumonia</td>
<td>10 mg/kg (max 400 mg) orally or IV, daily</td>
<td>Alternative to penicillin if allergic to penicillin</td>
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<tr>
<td>Nafcillin</td>
<td>Usual dose</td>
<td>25 mg/kg (max 1 g) orally, 6-hourly</td>
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<tr>
<td>Moderate infection</td>
<td>40 mg/kg (max 1.6 g) orally, 6-hourly</td>
<td></td>
<td></td>
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<tr>
<td>Severe infection</td>
<td>50 mg/kg (max 2 g) IV, 6-hourly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocarditis</td>
<td>50 mg/kg (max 2 g) IV, 4-hourly</td>
<td></td>
<td></td>
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<tr>
<td>Surgical prophylaxis</td>
<td>50 mg/kg (max 2 g) IV, as a single dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>HIV infection</td>
<td>30 mg/kg (max 1.25 g) orally, 8-hourly</td>
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<tr>
<td>HIV prophylaxis for high-risk exposures</td>
<td>&lt; 13 years: 55 mg/kg (max 2 g) orally, 12-hourly; &gt; 12 years 1250 mg orally, 12-hourly</td>
<td>For 4 weeks or until source shown to be HIV negative</td>
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<tr>
<td>Nitrofurantoin</td>
<td>Recurrent urinary tract infection prophylaxis</td>
<td>1–2.5 mg/kg (max 100 mg) orally, nightly</td>
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<tr>
<td>Norfloxacin</td>
<td>Usual dose</td>
<td>10 mg/kg (max 400 mg) orally, 12-hourly</td>
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</tr>
<tr>
<td>Nystatin</td>
<td>Oral candidiasis</td>
<td>1 mL of 100,000 units/mL suspension orally, 6-hourly</td>
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<tr>
<td>Oxacillin</td>
<td>Usual dose</td>
<td>25 mg/kg (max 1 g) orally, 6-hourly</td>
<td></td>
</tr>
<tr>
<td>Moderate infection</td>
<td>40 mg/kg (max 1.6 g) orally, 6-hourly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe infection</td>
<td>50 mg/kg (max 2 g) IV, 6-hourly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocarditis</td>
<td>50 mg/kg (max 2 g) IV, 4-hourly</td>
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<td></td>
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<tr>
<td>Surgical prophylaxis</td>
<td>50 mg/kg (max 2 g) IV, as a single dose</td>
<td></td>
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<tr>
<td>Penicillin</td>
<td>See benzathine penicillin or benzylpenicillin or phenoxymethylpenicillin or procaine penicillin</td>
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<tr>
<td>Pentamidine</td>
<td>PCP treatment</td>
<td>4 mg/kg IV, daily</td>
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<tr>
<td>PCP prophylaxis</td>
<td>4 mg/kg IV or nebulized, every 2–4 weeks</td>
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Table A.3.1 (Continued)

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Indication(s)</th>
<th>Dose (Do Not Exceed Adult Dose)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenoxyimethyl penicillin</td>
<td>Pharyngitis, tonsillitis</td>
<td>10 mg/kg (max 500 mg) orally,</td>
<td>12-hourly</td>
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<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Balanitis, cellulitis, erysipelas, impetigo</td>
<td>10 mg/kg (max 500 mg) orally,</td>
<td>6-hourly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post-splenectomy prophylaxis</td>
<td>≤2 years: 125 mg; 2 years or older: 250 mg orally, 12-hourly</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Recurrent rheumatic fever prevention</td>
<td>250 mg orally, 12-hourly</td>
</tr>
<tr>
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<tr>
<td>Piperacillin</td>
<td>Severe sepsis, including <em>Pseudomonas</em></td>
<td>100 mg/kg (max 4 g) IV, 8-hourly</td>
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<tr>
<td>Piperacillin+tazobactam</td>
<td>Severe sepsis, including <em>Pseudomonas</em></td>
<td>100 + 12.5 mg/kg (max 4 + 0.5 g) IV, 8-hourly</td>
<td></td>
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<tr>
<td></td>
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</tr>
<tr>
<td>Praziquantel</td>
<td><em>Schistosoma haematobium</em> infection, <em>S. mansoni</em> infection</td>
<td>20 mg/kg orally (two doses, 4 hourly apart)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>S. japonicum</em> infection, <em>S. mekongi</em> infection</td>
<td>20 mg/kg orally (three doses, 4 hourly apart)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Beef tapeworm, pork tapeworm</td>
<td>10 mg/kg orally, as a single dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dwarf tapeworm</td>
<td>25 mg/kg orally, as a single dose</td>
</tr>
<tr>
<td>Primaquine</td>
<td><em>Plasmodium vivax</em> (acquired outside Southeast Asia and the Pacific Islands), <em>P. ovale</em></td>
<td>0.3 mg/kg (max 15 mg) orally, daily</td>
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<tr>
<td></td>
<td><em>P. vivax</em> (acquired in Southeast Asia or the Pacific Islands)</td>
<td>0.5 mg/kg (max 30 mg) orally, daily with food OR if nausea occurs, 0.25 mg/kg (max 15 mg) orally, 12-hourly</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Procaine penicillin</td>
<td>Congenital or early syphilis</td>
<td>30 mg (50,000 U)/kg (max 1.5 g or 2.4 million U) IM, daily</td>
<td>For 10 days</td>
</tr>
<tr>
<td></td>
<td>Tertiary syphilis</td>
<td>60 mg (100,000 U)/kg (max 2.4 g or 4 million U) IM, daily</td>
<td>For 14 days</td>
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<tr>
<td></td>
<td>Cellulitis, erysipelas</td>
<td>50 mg (80,000 U)/kg (max 1.5 g or 2.4 million U) IM, daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bites and clenched fist injuries</td>
<td>50 mg (80,000 U)/kg (max 1.5 g or 2.4 million U) IM, as a single dose</td>
<td></td>
</tr>
<tr>
<td>Proguanil</td>
<td>Malaria prophylaxis</td>
<td>&lt;2 years: 50 mg, 2–6 years: 100 mg, 7–10 years: 150 mg, &gt;10 years: 200 mg orally, daily</td>
<td></td>
</tr>
<tr>
<td>Pyrantel</td>
<td>Threadworm</td>
<td>10 mg/kg (max 750 mg) orally, as a single dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hookworm, roundworm</td>
<td>20 mg/kg (max 750 mg) orally, as a single dose</td>
<td></td>
</tr>
<tr>
<td>Antimicrobial</td>
<td>Indication(s)</td>
<td>Dose (Do Not Exceed Adult Dose)</td>
<td>Notes</td>
</tr>
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<td>-------------------------------</td>
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<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Tuberculosis</td>
<td>25 mg/kg (max 1 g) orally daily OR 50 mg/kg (max 2 g) orally, thrice weekly</td>
<td></td>
</tr>
<tr>
<td>Pyrimethamine</td>
<td>Toxoplasma encephalitis or cysts</td>
<td>2.5 mg/kg (max 100 mg) orally, then 1 mg/kg (max 25 mg) orally, daily</td>
<td>Give daily folinic acid 5 mg (adult dose) or folic acid supplementation</td>
</tr>
<tr>
<td>Pyrimethamine + sulfadoxine</td>
<td><em>Plasmodium falciparum</em> malaria</td>
<td>6 weeks to &lt;1 year: 1/4 tablet, 1–3 years: 1 tablet, 4–8 years: 2 tablets orally, as a single dose (pyrimethamine + sulfadoxine 25 + 500 mg)</td>
<td></td>
</tr>
<tr>
<td>Quinine dihydrochloride</td>
<td>Severe <em>Plasmodium falciparum</em> malaria</td>
<td>Loading dose: 20 mg/kg (max 1.4 g) in 5% dextrose IV over 4 hourly OR 7 mg/kg (max 500 mg) IV over 30 min followed immediately by 10 mg/kg (max 700 mg) over 4 hourly</td>
<td>Maintenance dose: 10 mg/kg (max 700 mg) IV, 8-hourly over 4 hourly</td>
</tr>
<tr>
<td>Quinine sulfate</td>
<td>Uncomplicated <em>Plasmodium falciparum</em> malaria</td>
<td>10 mg/kg (max 600 mg) orally, 8-hourly</td>
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</tr>
<tr>
<td>Quinupristin/dalfopristin</td>
<td>Vancomycin-resistant enterococcal infection</td>
<td>7.5 mg/kg IV, 8-hourly</td>
<td></td>
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<tr>
<td>Rifabutin</td>
<td><em>M. avium</em> complex infection</td>
<td>5 mg/kg (max 300 mg) orally, daily</td>
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</tr>
<tr>
<td>Rifampin or rifampicin</td>
<td>Usual dose</td>
<td>10 mg/kg (max 600 mg) orally daily</td>
<td>Not recommended as sole antibiotic, because of rapid emergence of resistance</td>
</tr>
<tr>
<td></td>
<td>Tuberculosis</td>
<td>10 mg/kg (max 600 mg) orally daily OR 15 mg/kg (max 600 mg) orally, thrice weekly</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Haemophilus influenzae</em> type b meningitis prophylaxis</td>
<td>&lt; 1 month: 10 mg/kg; ≥1 month: 20 mg/kg (max 600 mg) orally, daily for 4 days</td>
<td></td>
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<tr>
<td></td>
<td><em>Neisseria meningitidis</em> prophylaxis</td>
<td>&lt; 1 month: 5 mg/kg; ≥1 month: 10 mg/kg (max 600 mg) orally, 12-hourly for 2 days</td>
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<tr>
<td></td>
<td>Brucellosis</td>
<td>15 mg/kg (max 600 mg) orally, daily</td>
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<tr>
<td>Roxithromycin</td>
<td>Usual dose</td>
<td>4 mg/kg (max 150 mg) orally, 12-hourly</td>
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<tr>
<td>Sulfadiazine</td>
<td>Toxoplasma encephalitis or cysts</td>
<td>50 mg/kg (max 1.5 g) orally, 6-hourly</td>
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<tr>
<td>Teicoplanin</td>
<td><em>Staphylococcus aureus</em> infections</td>
<td>10 mg/kg (max 400 mg) IV, 12-hourly for three doses, then 6 mg/kg (max 400 mg) IV, daily</td>
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<tr>
<td></td>
<td>Endocarditis prophylaxis</td>
<td>10 mg/kg (max 400 mg) IV, as a single dose</td>
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<tr>
<td>Antimicrobial</td>
<td>Indication(s)</td>
<td>Dose (Do Not Exceed Adult Dose)</td>
<td>Notes</td>
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</tr>
<tr>
<td>Terbinafine</td>
<td>Tinea capitis, tinea corporis, tinea cruris, tinea pedis, tinea unguium</td>
<td>&lt; 20 kg: 62.5 mg, 20–40 kg: 125 mg, ≥ 40 kg: 250 mg orally, daily</td>
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<tr>
<td>Ticarcillin</td>
<td>Severe sepsis, including <em>Pseudomonas</em></td>
<td>50 mg/kg (max 3g) IV, 6-hourly</td>
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<tr>
<td>Ticarcillin+ clavulanate</td>
<td>Usual dose for sepsis</td>
<td>50 + 1.7 mg/kg (max 3 + 0.1 g) IV, 6-hourly</td>
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</tr>
<tr>
<td></td>
<td><em>Pseudomonas sepsis</em></td>
<td>50 + 1.7 mg/kg (max 3 + 0.1 g) IV, 4-hourly</td>
<td></td>
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<tr>
<td>Tinidazole</td>
<td>Giardiasis, Trichomonas, post-sexual assault prophylaxis</td>
<td>50 mg/kg (max 2 g) orally, as a single dose</td>
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<tr>
<td></td>
<td>Amebiasis</td>
<td>50 mg/kg (max 2 g) orally, daily</td>
<td></td>
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<tr>
<td>Tobramycin</td>
<td><em>Pseudomonas sepsis</em></td>
<td>&lt; 10 years: 7.5 mg/kg, ≥ 10 years: 6 mg/kg IV, daily</td>
<td>Modify dose in renal failure monitor drug levels: for once-daily dosing, take level at 6–14 hourly and use nomogram (Appendix 2); and/or trough &lt; 1 mg/L; for 8-hourly dosing: aim for peak 5–10 mg/L and trough &lt; 2 mg/L</td>
</tr>
<tr>
<td></td>
<td>Cystic fibrosis</td>
<td>&lt; 5 years: 40 mg, 5–10 years: 80 mg, &gt; 10 years: 160 mg nebulized 12-hourly</td>
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<tr>
<td>Trimethoprim</td>
<td>Recurrent urinary tract infection prophylaxis</td>
<td>2 mg/kg (max 150 mg) orally, nightly</td>
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<tr>
<td></td>
<td>Cystitis, epididymoorchitis, pyelonephritis</td>
<td>4 mg/kg (max 150 mg) orally, 12-hourly</td>
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<tr>
<td>Trimethoprim+ sulfamethoxazole (co-trimoxazole)</td>
<td>Usual dose</td>
<td>4 + 20 mg/kg (max 160 + 800 mg) orally, 12-hourly</td>
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<tr>
<td>PCP treatment</td>
<td></td>
<td>5 + 25 mg/kg IV, 6-hourly</td>
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<tr>
<td>PCP prophylaxis</td>
<td></td>
<td>4 + 20 mg/kg (max 80 + 400 mg) or 8 + 40 mg/kg (max 160 + 800 mg) orally, daily or 4 + 20 mg/kg (max 80 + 400 mg) orally, thrice weekly</td>
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<tr>
<td><em>Isospora belli</em> gastroenteritis</td>
<td></td>
<td>4 + 20 mg/kg (max 160 + 800 mg) orally, 6-hourly</td>
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<tr>
<td><em>Listeria monocytogenes</em> meningitis</td>
<td></td>
<td>5 + 25 mg/kg (max 160 + 800 mg) IV, 6-hourly</td>
<td></td>
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<tr>
<td>Melioidosis</td>
<td></td>
<td>8 + 40 mg/kg (max 320 + 1600 mg) orally or IV, 12-hourly</td>
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</tr>
<tr>
<td>Antimicrobial</td>
<td>Indication(s)</td>
<td>Dose (Do Not Exceed Adult Dose)</td>
<td>Notes</td>
</tr>
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<td>----------------</td>
<td>-----------------------------------------------------------------------------</td>
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<tr>
<td>Vancomycin</td>
<td>Usual dose, e.g., methicillin-resistant Staphylococcus aureus or S. epidermidis infections</td>
<td>25 mg/kg [child &lt; 12 years 30 mg/kg] (max dose 1 g) IV, 12-hourly OR 15 mg/kg (max 600 mg) IV, 8-hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe infection, e.g., brain abscess, pneumococcal meningitis, severe sepsis</td>
<td>15 mg/kg (max 1 g) IV, 6-hourly OR 30 mg/kg (max 2 g) IV, 12-hourly</td>
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<td>Pseudomembranous colitis</td>
<td>10 mg/kg (max 125 mg) orally, 6-hourly</td>
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<td>Endocarditis prophylaxis, endophthalmitis, eye injuries</td>
<td>20 mg/kg (max 1 g) IV, as a single dose</td>
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<tr>
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<td>Surgical prophylaxis</td>
<td>15 mg/kg (max 1 g) IV, as a single dose</td>
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<tr>
<td>Voriconazole</td>
<td>Invasive pulmonary aspergillosis</td>
<td>6 mg/kg IV, 12-hourly for two doses, then 4 mg/kg IV or orally, 12-hourly</td>
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<tr>
<td>Zidovudine</td>
<td>HIV infection</td>
<td>10 mg/kg (max 300 mg) orally, 12-hourly</td>
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