# Evidence-based Pediatric Infectious Diseases

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# Contents

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**Elizabeth Elliott** is Professor of Paediatrics and Child Health, University of Sydney; Consultant Paediatrician, The Children's Hospital at Westmead; Director, Centre for Evidence Based Paediatrics, Gastroenterology and Nutrition; and Practitioner Fellow, National Health and Medical Research Council of Australia. She is Director of the Australian Paediatric Surveillance Unit and past Convenor of the International Network of Paediatric Surveillance Units. She is Senior Associate Editor and co-author of *Evidence Based Pediatrics and Child Health* (Moyer V, ed., BMJ Books 2000, 2nd edition, 2004).

**Ruth Gilbert** is Reader in Clinical Epidemiology at the Institute of Child Health, London, having completed her training in pediatrics. She has published extensively on the epidemiology of infectious diseases, both original papers and textbooks. She coordinates research programs on the evaluation of screening and diagnostic tests and treatment for congenital toxoplasmosis, and for neonatal group B streptococcal infection. She is coauthor of *Evidence-Based Pediatrics and Child Health*, by Moyer V et al. Ruth teaches evidence-based medicine, has published Cochrane reviews, and is a reviewer for the Cochrane Collaboration.

**Michael E. Pichichero** is Professor of Microbiology and Immunology, Pediatrics and Medicine at the University of Rochester in New York. He is board certified in pediatrics, in adult and pediatric allergy and immunology, and in pediatric infectious disease. Dr. Pichichero is a partner in the Elmwood Pediatric Group; a recipient of numerous awards, he has over 500 publications in infectious disease, immunology, and allergy. His major practice and research interests are in vaccine development, streptococcal infections, and otitis media.

**Virginia Moyer** is Professor of Pediatrics and Section Head, Academic General Pediatrics at Baylor College of Medicine and Texas Children's Hospital in Houston, Texas. Dr. Moyer has particular interests in teaching clinical epidemiology and studying the use of diagnostic tests in clinical care. She is a member of the Evidence-Based Medicine Working Group, the United States Preventive Services Task Force, and the International Advisory Board for the Cochrane Collaboration Child Health Field. She is Editor in Chief of the book *Evidence-Based Pediatrics and Child Health* (2nd edition), and the journal *Current Problems in Pediatrics and Adolescent Health Care*, and is a founding Associate Editor of *Evidence-Based Child Health: A Cochrane Review Journal*.

# Preface

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*

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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,[1–5] followed by lack of knowledge.[4,5] 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.[6] 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.[7] 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[7] 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[8] 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.clinicalevidence.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.[9] Most questions about treatment in this book are framed in the classic evidence-based PICO format,[9] 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.[8] The Cochrane reviewers

| | | | | |
|---|---|---|---|---|
| **Frame the question:** | Population | Intervention | Comparison | Outcome |
| | Children with sore throat or tonsillitis | Antibiotics | No antibiotics or placebo | Duration of illness or frequency of complications |
| **Search the literature:** | Cochrane Library: find a Cochrane review of antibiotics for sore throat in adults and children | | | |
| **Assess the evidence:** | Results:<br>• Six patients need to be treated with antibiotics to cure one extra sore throat at day 3<br>• Antibiotics reduce the frequency of complications<br>• Antibiotics more effective when patient has group A streptococcal infection<br>• Difficult to distinguish between adults and children in the studies, and no subgroup analysis of children was possible<br>• 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.

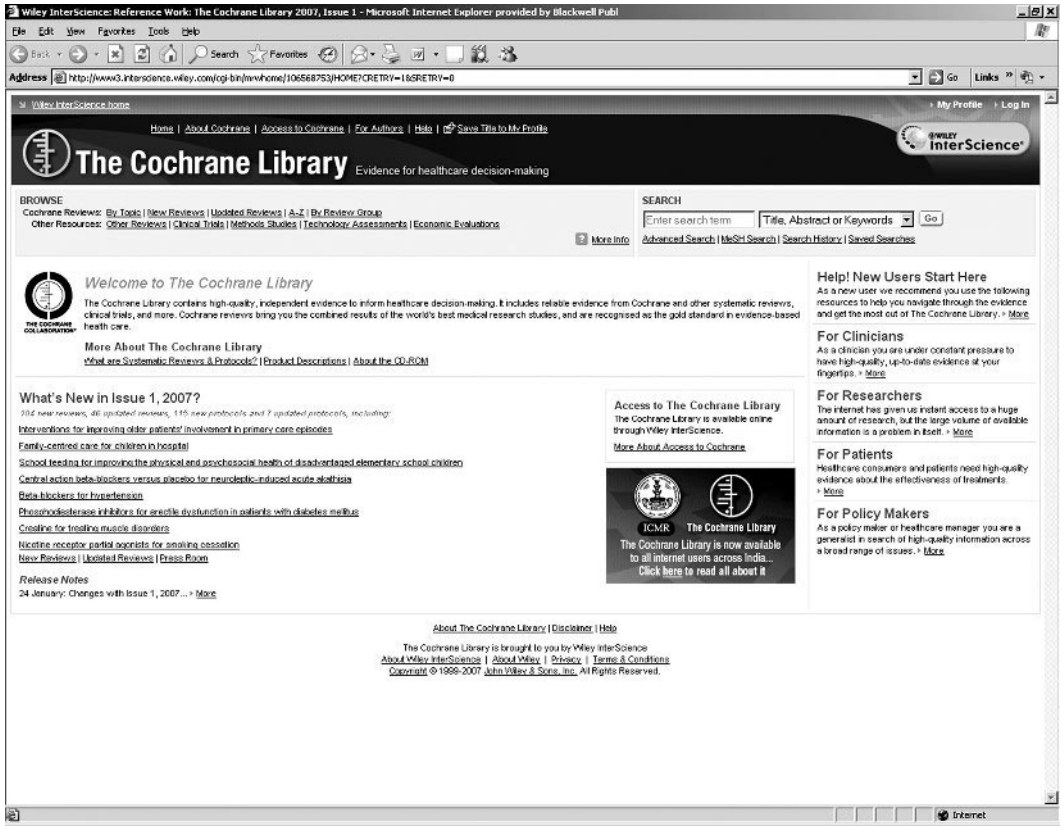


**Figure 1.2** The Cochrane Library home page.

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.[8] 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.

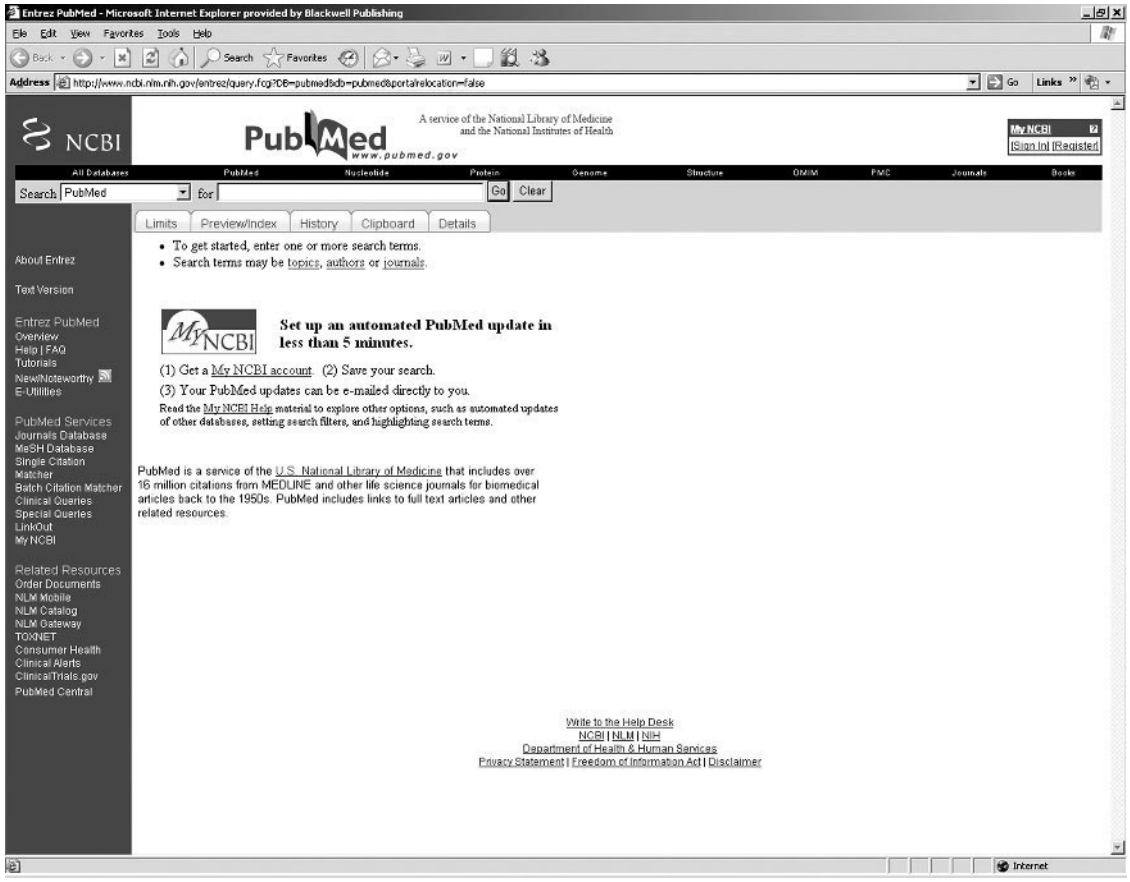


**Figure 1.3** PubMed home page.

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.

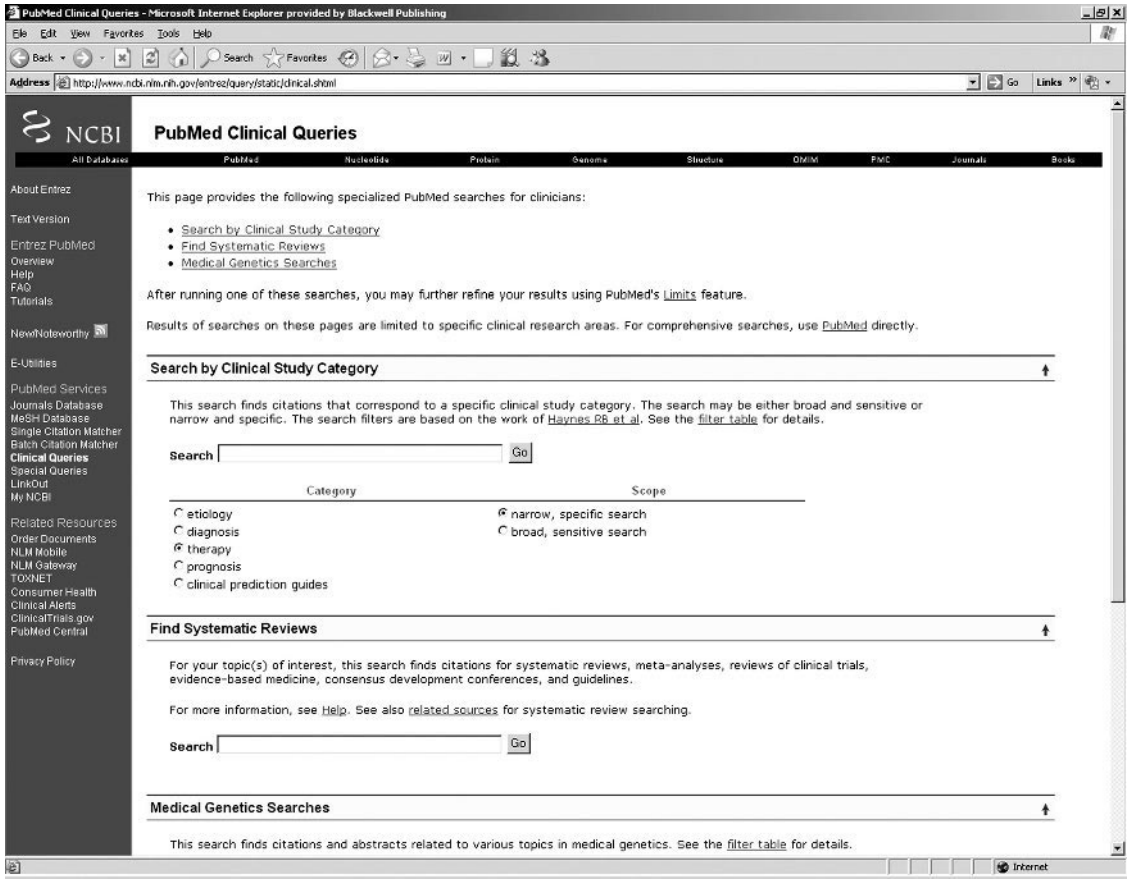


**Figure 1.4** PubMed "Clinical Queries" page.

## 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.[11] 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 1.1** Relationship between question type, study type, and best source of evidence.

| Question Type | Information Sought | Study Type | Best Source of Evidence |
|---|---|---|---|
| Treatment | Comparison of current best practice with a new therapy or comparison of new therapy with placebo | 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) | Cochrane Library<br>Clinical Evidence<br>Clinical practice guidelines<br>Medline (PubMed)<br>Evidence-based Web sites |
| Baseline risk (frequency) | Disease incidence; or disease prevalence; or frequency of complications | Population-based studies or cohort studies | Medline (PubMed)<br>Review articles<br>Textbooks |
| Etiology | Cause of disease | Cohort studies; case-control studies; RCTs when the question is about an adverse effect of an intervention | Cochrane Library<br>Clinical Evidence<br>Medline (PubMed) |
| Diagnosis | 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 | The best studies allow an independent blind comparison between the test and the reference ("gold") standard for diagnosis | Cochrane Library<br>Medline (PubMed) |
| Prognosis | Outcomes of disease: short and long term | Cohort studies or no treatment/placebo arm of RCTs | Medline (PubMed)<br>Textbooks |

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.

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# CHAPTER 2
# Rational antibiotic use

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.[1–5] 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.[7] The evidence suggested that the selective effect of azithromycin allowed the growth and transmission of preexisting, azithromycin-resistant strains.[7]

## 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.[5] 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[8]) and a population level.[9] 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.[10] 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.[11] 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.[12] 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.[12] Treatment with a beta-lactam for longer than 5 days was also associated with an increased risk of carriage.[12] 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[13] and *Pseudomonas aeruginosa.*[14]

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-sulfamethoxazole, 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.[15] 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.[15]

## 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.[16] While one study showed that topical ciprofloxacin was superior to framycetin in the short-term treatment of recurrent otorrhea,[17] a recent

report found that 17 children with recurrent otorrhea treated with topical ciprofloxacin were colonized with multidrug resistant *Pseudomonas* strains.[18] 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.[19]

### 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.[20] It has been suggested that one explanation could be the greater mucosal penetration of macrolides,[6] 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.[21]

A Cochrane review[21] 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.

### 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

### 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[22] 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.[22]

### 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.[23] 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,[24] 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 flucloxacillin, although there is no evidence that the combination is better than flucloxacillin alone. This risks increased toxicity as well as an increased chance of resistance, without likely clinical benefit.

## 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.

## 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.[23,24] Use of computer-generated prescriptions is estimated to result in 500,000 unnecessary prescriptions of amoxicillin, amoxicillin-clavulanate, cefaclor, or roxithromycin annually in Australia.[25]

## 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.

## 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.[26]

There is an increased incidence of infections in child-care facilities, often with resistant organisms. Hygiene measures can reduce the incidence of infections and the need for antibiotics.[27]

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# CHAPTER 3
# Cardiac infections

## 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

**Box 3.1 Organisms isolated from children with infective endocarditis (in approximate order of frequency[2,4,5]).**

- Viridans streptococci
- *Staphylococcus aureus*
- Enterococci
- HACEK group of Gram-negative bacilli:
  - *Haemophilus aphrophilus*
  - *Actinobacillus acinetomycetemcomitans*
  - *Cardiobacterium hominis*
  - *Eikenella corrodens*
  - *Kingella kingae*
- Non-toxigenic *Corynebacterium diphtheriae* (diphtheroids)
- Other Gram-negative bacilli, e.g., salmonella, haemophilus
- Coagulase negative staphylococci
- Miscellaneous (*Streptococcus pneumoniae*, fungi, *Bartonella*, *Coxiella*, etc.)
- Culture negative

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,[4] are caused by so-called viridans or alpha-hemolytic streptococci.[2,4,5] 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 Reyn[7] and Beth Israel criteria.[8] In these studies, children with proven endocarditis were assessed retrospectively to see if they fulfilled Duke[9] 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

Reviews[1,2] 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.[11] We found six RCTs in adults, five of staphylococcal endocarditis and only one of streptococcal endocarditis.[12] We found one meta-analysis of the role of adding aminoglycosides to a beta-lactam.[13] We found treatment guidelines for adults[1] and children[2] 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.[11] 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.[13] However, the quality of the studies was weak, and the confidence intervals wide.[13] 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.[12]

For short course therapy for right-sided *S. aureus* endocarditis in intravenous drug-users, cloxacillin alone was as effective as cloxacillin plus an aminoglycoside.[14]

The current recommendation for the initial empirical 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.[12–14]

The antibiotic regimens recommended below are, therefore, based mainly on expert opinion.[1,2,15,16]

## 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**

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

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**

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

The antibiotics should be changed, if necessary, to the most appropriate regimen as soon as the organism and its susceptibility pattern are known.

## 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.[12]

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),[15] although use of an established outpatient intravenous antibiotic therapy program is recommended.[16] 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.[15,16] 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.[1] 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).[1] Animal data and case reports[1,2] 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).[17] It is always recommended to give concomitant gentamicin for optimal bactericidal activity,[17] although there are no studies.[13] Antibiotic resistance is an increasing problem.[1,2] 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.[17]

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**

[NB: 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**

[NB: 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/nafcillin 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 evidence[14] 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**

[NB: 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.[23] *Neisseria gonorrhoeae* is another uncommon cause of endocarditis.[24] *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.[2,25]

## 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.[2] Medical therapy alone is usually unsuccessful, and most patients need surgery as well as antifungal agents.[2] 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.[2]

## 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*.[26] 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.[27]

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.[28] Q fever endocarditis requires a long course (at least 18 months) of combined therapy using doxycycline (>8 years) and hydroxychloroquine.[29]

## 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 cephalothin 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.