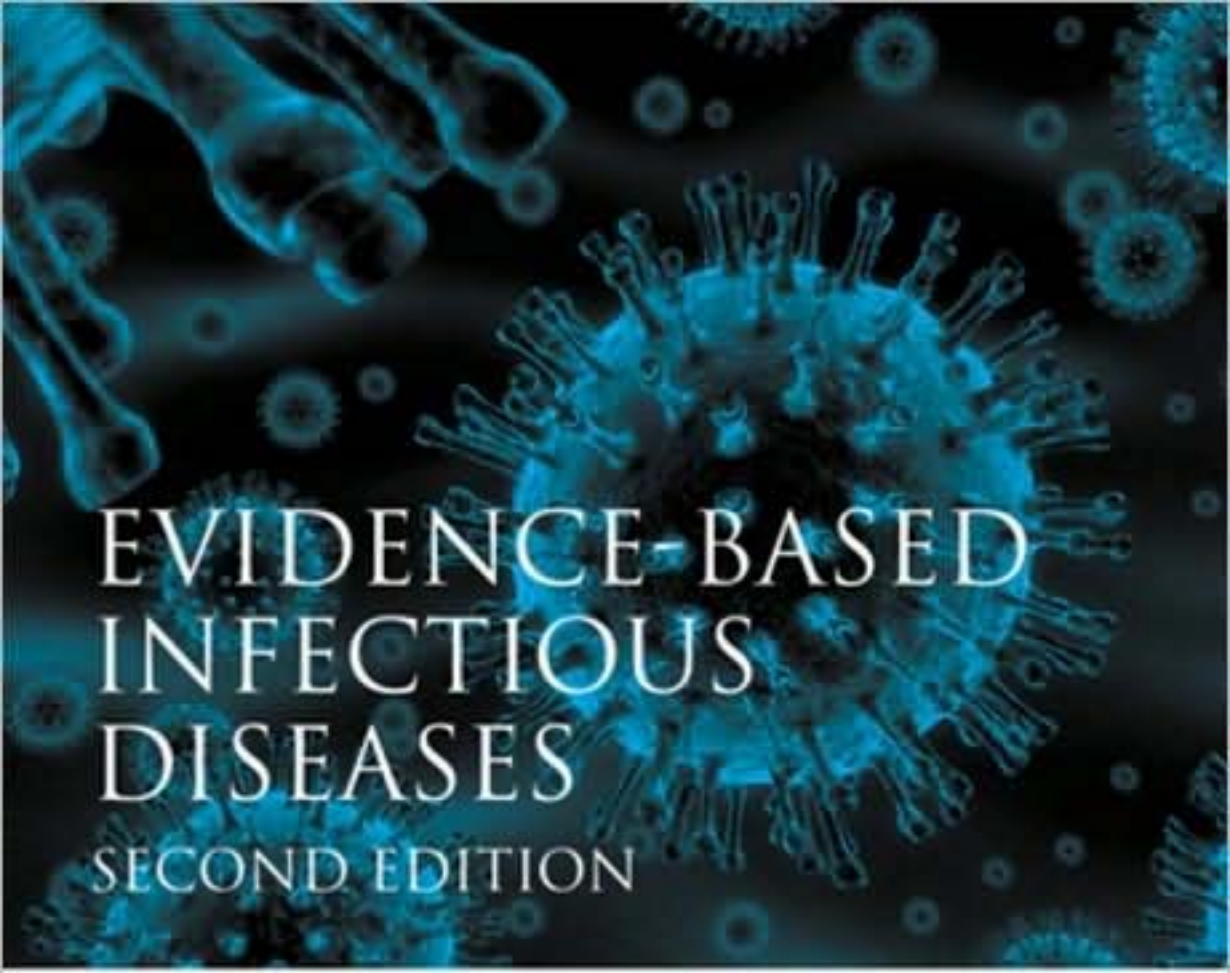

EVIDENCE-BASED INFECTIOUS DISEASES

SECOND EDITION

Edited by
Mark Loeb
Fiona Smaill
Marek Smieja

WILEY-BLACKWELL
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Evidence-Based Infectious Diseases

Evidence-Based Infectious Diseases, Second Edition
Edited by Mark Loeb, Fiona Smaill and Marek Smieja
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Evidence-Based Infectious Diseases

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Second Edition

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Preface to the First Edition

As busy academic physicians we are often approached about assuming new roles and responsibilities, and frankly are sometimes hesitant about placing yet another item on the "to do" list. However, when we were first approached about editing this book, our reaction was different. The idea of editing the first book about evidence-based infectious diseases was exciting. Although there are many standard textbooks on infectious diseases, none that we were aware of use an "evidence-based" approach.

We emphasize in this book both the methodological issues in assessing the quality of evidence, as well as the "best evidence" for practicing infectious diseases. We have divided the book into two parts. In Part I, we focus on specific infections, including skin and soft tissue infections, bone and joint infections, infective endocarditis, meningitis and encephalitis, community-acquired pneumonia, tuberculosis, diarrhea, urinary tract infections, sexually transmitted infections, and human immunodeficiency virus (HIV). In Part II, we focus on infections that occur in specific populations and settings. These include infection control, infections in the neutropenic host, surgical infections, the thermally injured patient, and infection in healthcare workers. We have asked chapter authors to begin with a clinical scenario, to help focus on relevant clinical questions, and then to briefly summarize the burden of illness or background epidemiology. The remainder of each chapter summarizes the best evidence with respect to diagnosis, prognosis, treatment, and prevention, with a focus, where possible, on systematic reviews.

As we discuss in the introductory chapter, we believe that important clinical questions that arise should be approached in a systematic fashion. The chapters in this book will never be as up to date as the information that you can derive by searching the most recent literature. This is particularly relevant when we are faced with new emerging infections, such as severe acute respiratory syndrome (SARS). However, browsing through these chapters will give a good context and will provide you with key evidence that you can update by conducting a search to see if there is any useful new information. While evidence from well-designed studies informs the decision-making process, it obviously does not replace it. The outcomes of a clinical trial, for example, may suggest a default antibiotic to use for pneumonia, but does not preclude our individualizing treatment based on patient allergies, the biology of the responsible organism, or the pharmacokinetics and pharmacodynamics of the drugs to be administered in that patient.

We hope that our approach will help to emphasize aspects of diagnosis, prognosis, treatment, or prevention in which there is already excellent evidence, while highlighting areas in which more compelling evidence is needed. In these latter areas in which our confidence is limited, the reader should be particularly careful to look for newer published data when faced with a similar clinical problem.

We are grateful to the chapter authors who made this book possible. We appreciate the guidance (and patience) of Christina Karaviotis and Mary Banks from BMJ Books. We thank our families (Andrea, Julia, and Nathalie Loeb; Cathy Marchetti and Daniel, Nicole, and Benjamin Smieja; Peter Seary) for their patience and support.

We hope you find this book informative and stimulating, and we shall certainly appreciate any feedback.

Mark Loeb
Marek Smieja
Fiona Smaill
Hamilton, 2004

Preface to the Second Edition

Following the success of our original edition in 2004, we are privileged to have this opportunity to edit an updated version of *Evidence-Based Infectious Diseases*. We have targeted this book to general internists and to trainees in infectious diseases, as feedback from the first edition indicated that our textbook was particularly helpful to these groups.

We hope that this new edition will bring added value, while continuing to serve as an evidence-based resource for physicians who manage patients with infections. Along with major updates in chapters on HIV, febrile neutropenia, bone and joint infections, sexually transmitted infections, urinary tract infections, and tuberculosis, there are three brand new chapters in this edition: Influenza, Critical care, and Infections in long-term care.

We are grateful to the chapter authors for all of their hard work. We would like to thank Mirjana Misina, Heather Addison, Rob Blundell, Laura Quigley, Beckie Brand, Lauren Brindley, and Mary Banks for their assistance in preparing this updated edition. We thank our families Andrea, Julia, and Nathalie Loeb; Cathy Marchetti and Benjamin, Nicole, and Daniel Smieja; and Peter Seary for their support.

We hope that you will find this edition informative and we welcome any feedback.

Mark Loeb
Marek Smieja
Fiona Smaill
Hamilton

CHAPTER 1

Introduction to evidence-based infectious diseases

Mark Loeb, Marek Smieja & Fiona Smaill

Our purpose in this chapter is to provide a brief overview of evidence-based infectious diseases practice and to set the context for the chapters which follow. We highlight evidence-based guidelines for assessing diagnosis, treatment, and prognosis, and discuss the application of evidence-based practice to infectious diseases, as well as identifying areas in which such application must be made with caution.

What is evidence-based medicine?

Evidence-based medicine was born in the writings of clinical epidemiologists at McMaster University, Yale, and elsewhere. Two series of guidelines for assessing the clinical literature articulated these, then revolutionary, ideas and found a wide audience of students, academics, and practitioners alike [1,2]. These guidelines emphasized the randomized clinical trial (RCT) for assessing treatment, now a standard requirement for the licensing of new drugs or other therapies. David Sackett, the founding chair of the Department of Clinical Epidemiology and Biostatistics at McMaster University, defined evidence-based medicine as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of patients" [3].

These guidelines, which we summarize later in the chapter, were developed primarily to help medical students and practicing doctors find answers to clinical problems. The reader was guided in assessing the published literature in response to a given clinical scenario, to find relevant clinical articles, to assess the validity and understand the results of the identified papers, and to improve their clinical practice. Aided by computers, massive databases, and powerful search engines, these guidelines and the evidence-based movement empowered a new generation of practitioners and have had a profound impact on how studies are conducted, reported, and summarized. The massive proliferation of randomized clinical trials, the increasing numbers of systematic reviews and evidence-based guidelines, and the emphasis on appropriate methods of assessing diagnosis and prognosis, have affected how we practice medicine.

Evidence-based infectious diseases

The field of infectious diseases, or more accurately the importance of illness due to infections, played a major role in the development of epidemiological research in the 19th and early 20th centuries. Classical observational epidemiology was derived from studies of epidemics – infectious diseases such as cholera, smallpox, and tuberculosis. Classical epidemiology was nevertheless action-oriented. For example, John Snow's observations regarding cholera led to his removal of the Broad Street pump handle in an attempt to reduce the incidence of cholera. Pasteur, on developing an animal vaccine for anthrax, vaccinated a number of animals with members of the media in attendance [4]. When unvaccinated animals subsequently died, while vaccinated animals did not,

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the results were immediately reported throughout Europe's newspapers.

In the era of clinical epidemiology, it is notable that the first true randomized controlled trial is widely attributed to Sir Austin Bradford Hill's 1947 study of streptomycin for tuberculosis [5]. In subsequent years, and long before the "large simple trial" was rediscovered by the cardiology community, large-scale trials were carried out for polio prevention, and tuberculosis prevention and treatment.

Having led the developments in both classical and clinical epidemiology, is current infectious diseases practice evidence-based? We believe the answer is "somewhat". We have excellent evidence for the efficacy and side effects of many modern vaccines, while the acceptance of before-and-after data to prove the efficacy of antibiotics for treating bacterial meningitis is ethically appropriate. In the field of HIV medicine we have very strong data to support our methods of diagnosis, assessing prognosis and treatment, as well as very persuasive evidence supporting causation. However, in treating many common infectious syndromes – from sinusitis and cellulitis to pneumonia – we have many very basic diagnostic and therapeutic questions that have not been optimally answered. How do we reliably diagnose pneumonia? Which antibiotic is most effective and cost-effective? Can we improve on the impaired quality of life that often follows such infections as pneumonia?

While virtually any patient presenting with a myocardial infarction will benefit from aspirin and thrombolytic therapy, there may not be a single "best" antibiotic for pneumonia. Much of the "evidence" that guides therapy in the infectious diseases, particularly for bacterial diseases, may not be clinical, but exists in the form of a sound biologic rationale, the activity of the antimicrobial against the offending pathogen, and the penetration at the site of infection (pharmacodynamics and pharmacokinetics). Still, despite having a sound biologic basis for choice of therapy, there are many situations where better randomized controlled trials need to be conducted and where clinically important outcomes, such as symptom improvement and health-related quality, are measured.

How, then, can we define "evidence-based infectious diseases" (EBID)? Paraphrasing David Sackett, EBID may be defined as "the explicit, judicious and conscientious use of current best evidence from infection diseases research in making decisions about the prevention and treatment of infection of individuals and populations". It is an attempt to bridge the gap between research evidence and the clinical practice of infectious diseases. Such an "evidence-based approach" may include critically appraising evidence for the efficacy of a vaccine or a particular antimicrobial treatment regimen. However, it may also involve finding the best evidence to support (or refute) use of a diagnostic test to detect a potential pathogen. Additionally, EBID refers to the use of the best evidence to estimate prognosis of an infection or risk factors for the development of infection. EBID therefore represents the application of research findings to help answer a specific clinical question. In so doing, it is a form of knowledge transfer, from the researcher to the clinician. It is important to remember that use of research evidence is only one component of good clinical decision-making. Experience and clinical skills are essential components. EBID serves to inform the decision-making process. For the field of infectious diseases, a sound knowledge of antimicrobials and microbiologic principles are also needed.

Posing a clinical question and finding an answer

The first step in practicing EBID is posing a clinically driven and clinically relevant question. To answer a question about diagnosis, therapy, prognosis, or causation, one can begin by framing the question [2]. The question usually includes a brief description of the patients, the intervention, the comparison, and the outcome (a useful acronym is "PICO"). For example, if asking about the efficacy of antimicrobial-impregnated catheters in intensive care units [6], the question can be framed as follows: "In critically ill patients, does use of antibiotic-impregnated catheters reduce central line infections?" After framing the question, the second step is to search the literature. There are increasingly a number of options for finding the best evidence. The first step might be to assess evidence-based synopses such as *Evidence-Based Medicine* or *ACP Journal Club* (we admit to bias – two of the editors [ML, FS] are associate editors for these journals). These journals regularly report on high-quality

studies that can impact practice. The essential components of the studies are abstracted and the papers are reviewed in an accompanying commentary by knowledgeable clinicians. However, since these journals are geared to a general internal medicine audience, many questions faced by clinicians practicing infectious diseases may not be addressed.

The next approach that we would recommend is to search for systematic reviews. Systematic reviews can be considered as concise summaries of the best available evidence that address sharply defined clinical questions [7]. Increasingly, the Cochrane Collaboration is publishing high-quality infectious diseases systematic reviews (http://www.cochranelibrary.com). Another source of systematic reviews is the *DataBase of Abstracts of Reviews of Effects* (DARE) (http://www.crd.york.ac.uk/crdweb). To help find systematic reviews, MEDLINE can be searched using the systematic review clinical query option in PubMed (http://www.ncbi.nlm.nih.gov/pubmed/). If there are no synopses or systematic reviews that can answer the clinical question, the next step is search the literature itself by accessing MEDLINE through PUBMED. After finding the evidence the next step is to critically appraise it.

Evidence-based diagnosis

Let us consider the use of a rapid antigen detection test for group A streptococcal infection in throat swabs. The first question to ask is whether there was a blinded comparison against an accepted reference standard. By blinded, we mean that the measurements with the new test were done without knowledge of the results of the reference standard.

Next, we would assess the results. Traditionally, we are interested in the sensitivity (proportion of reference-standard positives correctly identified as positive by the new test) and specificity (the proportion of reference-standard negatives correctly identified as negative by the new test).

Ideally, we would also like to have a measure of the precision of this estimate, such as a 95% confidence interval on the sensitivity and specificity, although such measures are rarely reported in the infectious diseases literature.

Note, however, that while the sensitivity and specificity may help a laboratory to choose the best test to offer for routine testing, they do not necessarily help the clinician. Thus, faced with a positive test with known 95% sensitivity and specificity, we cannot infer that our patient with a positive test for group A streptococcal infection has a 95% likelihood of being infected. For this, we need a positive predictive value, which is calculated as the percentage of true positives among all those who test positive. If the positive predictive value is 90%, then a positive test would suggest a 90% likelihood that the person is truly infected. Similarly, the negative predictive value is the percentage of true negatives among all those who test negative. Both positive and negative predictive value change with the underlying prevalence of the disease, hence such numbers cannot be generalized to other settings.

A more sophisticated way to summarize diagnostic accuracy, which combines the advantages of positive and negative predictive values while solving the problem of varying prevalence, is to quantify the results using likelihood ratios. Like sensitivity and specificity, likelihood ratios are a constant characteristic of a diagnostic test, and independent of prevalence. However, to estimate the probability of a disease using likelihood ratios, we additionally need to estimate the probability of the target condition (based on prevalence or clinical signs). Diagnostic tests then help us to shift our suspicion (pretest probability) about a condition depending on the result. Likelihood ratios tell us how much we should increase the probability of a condition for a positive test (positive likelihood ratio) or reduce the probability for a negative test (negative likelihood ratio). More formally, likelihood ratio positive (LR+) and negative (LR−) are defined as:

$$\mathrm{LR}+ = \frac{\text{odds of a positive test in an individual with the condition}}{\text{odds of a positive test in an individual without the condition}}$$

$$\mathrm{LR}- = \frac{\text{odds of a negative test in an individual with the condition}}{\text{odds of a negative test in an individual without the condition}}$$

A positive likelihood ratio is also defined as follows: sensitivity/(1 – specificity). Let us assume, hypothetically, that the sensitivity of the rapid antigen test is 80% and the specificity 90%. The positive likelihood ratio for the antigen test is (0.8/0.1) or 8. This would mean that a patient with a positive antigen test would have 8 times the odds of being positive compared with a patient without group A streptococcal infection. The tricky part in using likelihood ratios is to convert the pretest probability (say 20% based on our expected prevalence among patients with pharyngitis in our clinic) to odds: these represent 1:4 odds. After multiplying by 8, we have odds of 8:4, or a 67% post-test probability of disease. Thus, our patient probably has group A streptococcus, and it would be reasonable to treat with antibiotics.

The negative likelihood ratio, defined as (1 – sensitivity)/specificity, tells us how much we should reduce the probability for disease given a negative test. In this case, the negative likelihood ratio is 0.22, which can be interpreted as follows: a patient with pharyngitis and a negative antigen test would have their odds of disease multiplied by 0.22. In this case, a pretest probability of 20% (odds 1:4) would fall to an odds of 0.22 to 4, or about 5%, following a negative test. Nomograms have been published to aid in the calculation of post-test probabilities for various likelihood ratios [8].

Having found that the results of the diagnostic test appear favorable for both diagnosing or ruling out disease, we ask whether the results of a study can be generalized to the type of patients we would be seeing. We might also call this "external validity" of the study. Here we are asking the question: "Am I likely to get the same good results as in this study in my own patients?" This includes such factors as the severity and spectrum of patients studied versus those we will encounter in our own practice, and technical issues in how the test is performed outside the research setting.

To summarize, to assess a study of a new diagnostic test, we identify a study in which the new test is compared with an independent reference standard; we examine its sensitivity, specificity, and positive and negative likelihood ratios; and we determine whether the spectrum of patients and technical details of the test can be generalized to our own setting.

In applying these guidelines in infectious diseases, there are some important caveats.

- There may be no appropriate reference standard.
- The spectrum of illness may dramatically change the test characteristics, as may other co-interventions such as antibiotics.

For example, let us assume that we are interested in estimating the diagnostic accuracy of a new commercially available polymerase chain reaction (PCR) test for the rapid detection of *Neisseria meningitidis* in spinal fluid. The reference standard of culture may not be completely sensitive. Therefore, use of an expanded reference ("gold") standard might be used. For example, the reference standard may be growth of *N. meningitidis* from the spinal fluid, demonstration of an elevated white blood cell count in the spinal fluid along with gram-negative bacilli with typical morphology on Gram stain, or elevated white blood cell count along with isolation of *N. meningitidis* in the blood.

It is also important to know in what type of patients the test was evaluated, such as the inclusion and exclusion criteria, as well as the spectrum of illness. Given that growth of microorganisms is usually progressive, test characteristics in infectious diseases can change depending when the tests are conducted. For example, PCR conducted in patients who are early in their course of meningitis may not be sensitive as compared to patients that presented with late-stage disease. This addresses the issue of spectrum in test evaluation.

Evidence-based treatment

The term "evidence-based medicine" has become largely synonymous with the dictum that only randomized, double-blinded clinical trials give reliable estimates of the true efficacy of a treatment. For the purposes of guidelines, "levels of evidence" have been proposed, with a hierarchy from large to small RCTs, prospective cohort studies, case–control studies, and case series. In newer iterations of these "levels of evidence", a metaanalysis of RCTs (without statistical heterogeneity, indicating that the trials appear to be estimating the same treatment effect), are touted as the highest level of evidence for a therapy.

In general, clinical questions about therapy or prevention are best addressed through randomized controlled trials. In observational studies, since the choice of treatment may have been influenced by extraneous

factors which influence prognosis (so-called "confounding factors"), statistical methods are used to "adjust" for identified potentially confounding variables. However, not all such factors are known or accurately measured. An RCT, if large enough, deals with such extraneous prognostic variables by equally apportioning them to the two or more study arms by randomization. Thus, both known and unknown confounders are distributed roughly evenly between the study arms.

For example, a randomized controlled trial would be the appropriate design to assess whether dexamethasone administered prior to antibiotics reduces mortality in adults who have bacterial meningitis [9]. We would evaluate the following characteristics of such a study: who was studied; was there true random assignment; were interventions and assessments blinded; what was the outcome; and can we generalize to our own patients?

When evaluating clinical trials it is important to ensure that assignment of treatment was truly randomized. Studies should describe exactly how the patients were randomized (e.g., random numbers table, computer generating). It is also important to assess whether allocation of the intervention was truly concealed. It is especially important here to distinguish allocation concealment from blinding. Allocation of an intervention can always be concealed even though blinding of investigators, participants or outcome assessors may be impossible. Consider an RCT of antibiotics versus surgery for appendicitis (improbable as this is). Blinding participants and investigators after patients have been randomized would be difficult (sham operations are not considered ethical). However, allocation concealment occurs before randomization. It is an attempt to prevent selection bias by making certain that the investigator has no idea to what arm (antibiotics versus surgery) the next patient enrolled will be randomized. In many trials this is done through a centralized randomized process whereby the study investigator is faxed the assignment after the patient has been enrolled. In some trials, the assignment is kept in envelopes. The problem with this is that, if the site investigator (or another clinician) has a preference for one particular intervention over another, the possibility for tampering exists. For example, if a surgeon who is a site investigator is convinced that the patient he has just enrolled would benefit most from surgery, the surgeon might be tempted to hold the envelope up to a strong light, determine the allocation, and then select another if the contents of the envelope do not indicate surgery as the allocation. This would lead to selection bias and distort the result of the clinical trial. This type of tampering has been documented [10].

The degree of blinding in a study should also be considered. It is important to recognize that blinding can occur at six levels: the investigators, the patients, the outcome assessors, adjudication committee, the data monitoring committee, the data analysts, and even the manuscript writers (although in practice few manuscripts are written blinded of the results) [11]. Describing a clinical trial as "double-blinded" is vague if in fact blinding can occur at so many different levels. It is better to describe who was blinded than using generic terms.

Similarity of groups at baseline should also be considered when evaluating randomized controlled trials to assess whether differences in prognostic factors at baseline may have had an impact on the result. A careful consideration of the intervention is also important. One can ask what actually constitutes the intervention – was there a co-intervention that really may have been the "active ingredient"?

Follow-up is another important issue. It is important to assess whether all participants who were actually randomized are accounted for in the results. A rule of thumb is that the potential for the results to be misleading occurs if fewer than 80% of individuals randomized are not accounted for at the end (i.e., loss to follow-up of over 20% of participants). More rigorous randomized controlled trials are analyzed on an intention-to-treat basis. That is, all patients randomized are accounted for and are analyzed with respect to the group to which they were originally allocated. For example, an individual in our hypothetical appendicitis trial who was initially randomized to antibiotics but later received surgery would be considered in the analysis to have received antibiotics.

Having assured ourselves that the study is randomized, the randomization allocation was not prone to manipulation, and the randomized groups have ended up as comparable on major prognostic factors, we next examine the actual results. Consider a randomized controlled trial of two antibiotics A and B for community-acquired pneumonia. If the mortality rate with antibiotic A is 2% and that with B is

4%, the absolute risk reduction is the difference between the two rates (2%), the relative risk of A versus B is 0.5, and the relative risk reduction is 50%, that is the difference between the control and intervention rate (2%) divided by the control rate (4%). In studies with time-to-event data, the hazard ratio is measured rather than the relative risk, and can be thought of as an averaged relative risk over the duration of the study. Absolute risk reduction, relative risk, and hazard ratios are all commonly reported with a 95% confidence interval (CI) as a measure of precision. A 95% CI that does not cross 1.0 (for a relative risk or hazard ratio) or 0 (for the absolute risk reduction) has the same interpretation as a P value of < 0.05: we declare these results as "statistically significant". Unlike the P value, the 95% CI gives us more information regarding the size of the treatment effect. Note that statistical significance simply tells us whether the results were likely due to chance; the CI also tells us the precision of the estimate (helpful especially for underpowered studies, in which the wide CI warns us that a larger study may be required to more precisely determine the effect). It is important to be aware that statistical significance and clinical importance are not synonymous. A small study may miss an important clinical effect, whereas a very large study may reveal a small but statistically significant difference of no clinical importance. In well-designed studies, researchers prespecify the size of a postulated "minimum clinically important difference" rather than solely relying on statistical significance.

Measures of relative risk, hazard ratios, or absolute risk reduction may be difficult to apply in clinical practice. A more practical way of determining the size of a treatment effect is to translate the absolute risk reduction into its reciprocal, the number needed to treat (NNT). In this example, the number needed to treat is the number of patients who need to be treated to prevent one death. It is the inverse of the absolute risk reduction (1/0.02), which is 50. Therefore, if 50 patients are treated with antibiotic B instead of A, one death would be prevented. A 95% CI can be calculated on the NNT, although we would only recommend such calculations for statistically significant treatment effects. This recommendation is based on the curious mathematical property that, as the absolute risk reduction crosses 0, the NNT becomes infinite, and thereafter crosses over into the bounds of a "number needed to harm".

It is important to determine if all important outcomes were considered in the randomized controlled trial. For example, a clinical trial of a novel immunomodulating agent for patients with severe West Nile virus disease would need not only to consider neurologic signs and symptoms but also to assess functional status and health-related quality of life. When deciding whether the results of a randomized trial can be applied to your patients, the similarity in the setting and patient population needs to be considered. Finally, you must consider whether the potential benefits of the therapy outweigh the potential risks.

Rather than relying on individual RCTs, it is generally preferable to try to identify systematic reviews on the topic. Systematic reviews, however, also need to be critically evaluated. First, one must ensure that the stated question of the review addresses the clinical question that you are asking. The methods section should describe how all relevant studies were found: that is, including the specific search strategy as well as the inclusion and exclusion criteria. Study validity should be assessed, although there is no universally accepted method for scoring validity in systematic reviews. Both size and precision of treatment effects need to be considered. Similar to evaluating randomized controlled trials, whether all important outcomes were assessed in the review is important. Asking whether the findings are generalizable to your patients and whether the likely benefits are worth the potential harms and benefits is also important.

In summary, to assess a treatment we would find a systematic review or clinical trial; assess whether patients were properly randomized; whether various components of the study were blinded; whether there was a high proportion followed up for all clinically relevant outcomes. We then consider the actual results, and express these ideally as a "number needed to treat" to appreciate the importance (or lack thereof) for individual patients. Finally, we consider whether these results are applicable to the type and severity of disease that we may see in our clinics.

In examining a treatment in infectious diseases, a few caveats to these guidelines are in order.

- For many infections there may be a very strong historic and biologic rationale to treat; in such cases an RCT using placebo will be unethical.
- Many infections may be too rare to study in RCTs, and some infected populations (such as injection

drug users) may be difficult to enrol into treatment studies. Observational methods, such as case–control or cohorts to examine therapies or durations associated with cure or relapse, may be the most appropriate methods in these circumstances.

- While the individually randomized clinical trial is held up as an ideal, it may be more sensible to study many infections through so-called "cluster randomization" in which the unit of randomization may be the hospital, a school, neighborhood, or family. Such studies may detect a treatment effect where herd immunity is important, and may be more feasible to run. However, the confidence intervals for a cluster-randomized study are somewhat wider than if individuals are randomized.
- Even when individually randomized, the infection itself may represent a "cluster". Thus, a highly effective therapy for one strain of multidrug resistant (MDR) *M. tuberculosis* may be useless against another MDR strain. Hence, biologic knowledge of the pathogen and therapy need to be considered when the results of an RCT are generalized to a particular clinical setting.

Evidence-based assessment of prognosis

Many studies about risk factors and outcomes for infectious diseases are published but the quality is variable. The best designs for assessing these are cohort studies in which a representative sample of patients is followed, either prior to developing the infection (to determine risk) or after being infected (to determine outcome). Patients should be assembled at a similar point in their illness (the so-called "inception cohort"), and follow-up should be sufficiently long and complete. Important prognostic factors should be measured, and adjusted for in the analysis. As with clinical trials, the outcome measures are a relative risk, absolute risk, or hazard ratio associated with a particular infection or prognostic factor. For example, to assess the outcome of patients with severe acute respiratory syndrome (SARS), one would optimally want an inception cohort of individuals who meet the case definition within several days of onset of symptoms. These individuals would then be followed prospectively. One of the challenges with SARS was the lack of a "realtime" diagnostic test with high sensitivity and specificity. In general, as diagnostic tests improve, our ability to detect early disease will improve. If SARS re-emerges and therapeutic agents are developed, this will change the natural history, hence the importance of noting whether therapy was administered in the cohort study. If strains of SARS coronavirus mutate as immunity to the virus builds, this may reduce the virulence of the agent. Therefore, it is important to keep in mind that estimates of risk and outcome may change with changes in the infectious agent.

Summary

We hope that the approaches described in this chapter will prove useful for evaluating articles about diagnosis, prognosis, treatment, or prevention in the infectious diseases literature. Using the principles described in this chapter, the chapters that follow attempt to summarize the best evidence for key clinical issues about infectious diseases.

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PART 1
Specific diseases

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CHAPTER 2
Skin and soft-tissue infections

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Impetigo

Impetigo is a common skin infection distributed worldwide. *Staphylococcus aureus* and β-hemolytic streptococci are invariably the pathogens [1]. Typically, streptococcal impetigo (nonbullous impetigo) starts as papules, turning to pustules that break down to form the characteristic "honey-coloured" crust. Bullous impetigo is more commonly associated with staphylococci. In this form, vesicles first appear that then evolve to larger bullae and eventually rupture leaving a shiny thin brown "varnish-like" crust. Usually the lesions are on exposed areas of the body, typically face and extremities. Generally streptococci have recently colonized the skin and then subsequently been inoculated into the dermis by a minor trauma, whereas staphylococcal impetigo is associated with colonization of the nares [2]. There can be transmission to other persons with close personal contact, such as athletes [3]. Infection occurs most frequently in children of lower socioeconomic groups. Impetigo is seen year round in warmer climates and in the summer months in northern climates [2]. Patients with impetigo rarely have systemic signs of infection.

There is evidence from a systematic review and metaanalysis that treatment with topical antibiotics is more effective than placebo (odds ratio [OR] 2.69, 95% confidence interval [CI] 1.49–4.86) [4]. There is no significant difference between the effects of mupirocin and fusidic acid (OR 1.7, 95% CI 0.77–4.03) [4]; however, strains of *S. aureus* resistant to mupirocin are being found [5]. A Cochrane review concluded that topical mupirocin was superior to oral erythromycin (OR 1.22, 95% CI 1.05–2.97), but in most other comparisons topical and oral antibiotics did not show different cure rates [6]. A penicillinase-resistant penicillin, a first-generation cephalosporin or a macrolide are recommended for oral therapy [7] but local resistance patterns, for example, prevalence of erythromycin-resistant *S. aureus* and *Streptococcus pyogenes*, should be taken into account in the choice of antibiotic. In cases of a nonresolving impetigo, infection may be with community-acquired methicillin resistant *S. aureus* (MRSA). See later in this chapter for further discussion on community-acquired MRSA infections.

Cellulitis and erysipelas

Case presentation 1

A healthy 45-year-old man hit his forearm while doing some house renovations, causing a minor abrasion 3 days prior to his presentation to the Emergency Department. He noted some minor swelling, pain, and erythema yesterday, but this morning he noted much more pain. His right forearm was swollen and erythema covered most of the dorsal surface from wrist to elbow. The emergency physician refers him for consideration of parenteral therapy and inpatient treatment with concerns about the area of involvement and rate of spread. His health is otherwise excellent.

On examining the patient, he is afebrile, pulse rate of 78 per minute and blood pressure of 134/75 mmHg. He has a small abrasion on his dorsal wrist with erythema extending to the elbow. The erythema is not raised, has indistinct borders, with no vesicles or bullae. The lesion is warm, tender to palpation, but there is no increase in pain on movement.

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Cellulitis is a common problem in primary care but only a minority are referred to consultants or admitted for inpatient treatment. A review of a patient database in five urban hospitals showed 3929 diagnoses of cellulitis representing 1·3% of Emergency Department visits; 7% required inpatient treatment [8].

Cellulitis usually presents with pain, erythema with typically indistinct borders, and swelling. Fever and regional lymphadenitis are occasionally seen. In a predominately outpatient population, pain, erythema, and swelling were described in 69%, 78%, and 69% of cases, respectively, while fever and lymphadenitis occurred in only 7% and 10% of patients [8]. For an inpatient population, pain, erythema, and swelling were seen in 87%, 79%, and 90%, respectively, and fever occurred in 63% of patients [9]. Unfortunately, these signs and symptoms are not specific and many other processes can present with similar clinical findings, for example superficial or deep vein thrombophlebitis, fasciitis, hematoma, dermatitis, and local reaction to a bite or sting.

Most commonly *S. aureus* and *S. pyogenes* are the pathogens. Less often and usually associated with underlying chronic disease, immunosuppression, or infection at a particular site (e.g., periorbital cellulitis with sinusitis), pathogens can include *Haemophilus influenzae*, *Pseudomonas aeruginosa*, other *Streptococcus* spp., gram-negative bacilli, *Clostridium* spp., and other anaerobes [10,11]. In a data registry of hospitalized patients in Canada and the USA, 1562 bacterial isolates were identified over 1 year in a wide variety of patients with skin and soft-tissue infections: *S. aureus* accounted for 42·6% of isolates, with 24% being MRSA, *P. aeruginosa* (11·3%), *Enterococcus* spp. (8·1%), *Escherichia coli* (7·2%), *Enterobacter* spp. (5·2%), and β-hemolytic streptococci (5·1%) [12]. Essentially the same rank was seen in both countries with the exception of *Enterococcus* spp. which was third in the USA and seventh in Canada [12]. If there is a concern with exposure to water, certain specific organisms should be considered. In salt water, *Vibrio vulnificus* can cause a cellulitis and a potentially life-threatening infection in patients with liver disease. In fresh water, *Aeromonas hydrophilia* is a possible pathogen.

Erysipelas is a distinctive form of cellulitis. The lesion is typically bright red, warm, painful (which differentiates it from more superficial infections) with a raised, clearly demarcated border (usually not seen in other forms of cellulitis). Facial erysipelas with the often described malar "butterfly" rash actually represents only 15–20% of cases and most infections involve the lower extremity [10,11]. Systemic symptoms, for example fever, chills, sweats and rigors, are common. Infants, young children, and older adults are most commonly affected [13]. Erysipelas has a predisposition for areas of impaired lymphatic drainage and in these patients recurrent episodes can occur [11]. Group A streptococcus (*S. pyogenes*) is primarily responsible for erysipelas but groups B, C, and G, as well as *S. aureus* have been described [12]. Only 5% of blood cultures are positive [10].

Surface cultures, aspiration, and blood cultures all have low diagnostic yield in identifying the infecting organism causing cellulitis. Surface cultures are not recommended because of low yield and contamination with skin flora. Some advocate culturing an intact pustule if present [10]. Several studies have described varying techniques to aspirate from the lesion, resulting in positive cultures from 10% to 100% of the time [14–17]. In a large retrospective study of over 750 patients with cellulitis and 553 blood cultures, only 2% of blood cultures yielded a pathogen, and 73% of these were β-hemolytic streptococci [18]. In the healthy patient without an unusual exposure, microbiologic testing is neither necessary nor cost-effective.

Routine laboratory investigations have little diagnostic role in managing the healthy patient with cellulitis but may be required in the management of patients with chronic diseases, such as diabetes, liver disease, or renal failure, where an infection may lead to acute deterioration of the underlying disease, influencing the choice and dose of antibiotics and the decision whether to admit. Plain radiographs to rule out a foreign body are sometimes needed. Often radiographs are obtained to screen for tissue air if necrotizing fasciitis is a concern, or for osteomyelitis in an infected diabetic foot ulcer.

In mild and localized cellulitis in otherwise healthy patients presenting to the Emergency Department, an oral agent covering *S. aureus* and *Streptococcus* spp. is sufficient, and there is no advantage to agents with broader spectrum antimicrobial activity [19]. A penicillinase-resistant penicillin, first- or second-generation cephalosporin, or macrolide have

Case presentation 1 (continued)

After careful review you decide this patient has cellulitis and unlikely has a fasciitis. Since he is otherwise healthy with no history of unusual exposure you feel no extra tests are required. You are, however, concerned about the size and the rapidity of spread and decide this patient needs parenteral antibiotics, but which one(s) and does he need to be admitted?

appropriate activity, although no studies demonstrating superiority of one agent over another have been done. While a 7- to 10-day course of therapy with the agent at its higher dose range is recommended, there is little evidence on which to base the duration of therapy or the optimal dose. In a randomized controlled trial of levofloxacin 500 mg/day in patients with uncomplicated cellulitis, 5 days of therapy was as effective as 10 days of therapy [20]. Cellulitis recurs in some patients and in a retrospective, population-based cohort study, tibial involvement, history of cancer, and dermatitis predicted recurrence (hazard ratios of 5.02, 3.87, and 2.99 respectively) [21]. Prophylactic penicillin is recommended for patients with recurrent episodes, although one study showed that this approach was only effective in patients without predisposing factors [22,23].

In patients with more severe cellulitis, it is generally accepted that parenteral antibiotics are required. What is not well defined is in which patients cellulitis should be deemed moderate or severe. Studies of moderate or severe cellulitis have included patients with cellulitis and one or more of the following: extensive area, ulceration, abscess, signs of toxicity or sepsis, associated with surgical site, bite, foreign body, trauma, intravenous drug injection site, diabetic foot or pressure ulcer, immunosuppression (e.g. HIV), diabetes, chronic corticosteroid use, or failure of previous therapy [24–30].

Many antibiotic regimens evaluated in methodologically sound studies have demonstrated similar efficacy with inpatient populations and complicated skin infections: pipercillin-tazobactam [24], ticarcillin-clavulanate [24,25], levofloxacin [25,31], teicoplanin [32,33], meropenem [26], imipenem/cilastin [26], ceftriaxone [30,33–36], ciprofloxacin [28], ofloxacin [27], cefotaxime [27,28], linezolid [29], oxacillin [29], and cefazolin [35,36]. Clinical cure rates ranged from 84% to 98·4% and microbiological cure rates from 71% to 94%. In a metaanalysis that compared the effectiveness and safety of fluoroquinolones versus β-lactams for the empirical treatment of skin and soft-tissue infections that included 20 randomized controlled trials, fluoroquinolones were more effective than β-lactams for the clinically evaluable patients (OR 1.29, 95% CI 1.00–1.66) but not for patients with moderate to severe infections (OR 1.12, 95% CI 0.80–1.55) [37]. However, the authors concluded that because of the high proportion of successfully treated patients in both groups and more adverse effects associated with fluoroquinolones, fluoroquinolones did not have a substantial advantage compared with β-lactams. In a randomized controlled trial of patients with lower limb cellulitis requiring intravenous antibiotics, there was no evidence to support the addition of intravenous benzylpenicillin to intravenous flucloxacillin (difference in mean number of doses −0.24, 95% CI −2.48 to 2.01, $P = 0.83$) [38].

Many patients may choose to be treated with parenteral therapy on an outpatient basis. Prospective evaluations of outpatient antibiotic programs have shown that they are safe and effective [30,33–36,39] and a randomized controlled trial of intravenous antibiotics at home or in hospital for treatment of cellulitis demonstrated no difference in outcome between the two groups (mean difference in days to no advancement of cellulitis 0.01 days, 95% CI −0.3 to 0.28) [40]. Patient satisfaction was greater in patients treated at home.

Intravenous ceftriaxone has been widely recommended for outpatient therapy owing to its once daily dosing [30,34]. Two randomized studies have demonstrated that cefazolin and probenecid have equivalent efficacy to ceftriaxone in an outpatient setting [35,36]. Brown et al. randomized 194 patients with moderate to severe cellulitis to 2 g intravenous cefazolin daily or 2 g intravenous ceftriaxone daily, while both groups received probenecid 1 g orally [35]. Outcomes were similar, 91·8% versus 92·7% clinical cure, with cost savings associated with the cefazolin group. However, the majority of patients were intravenous drug users with injection site infections, follow-up was not complete and patients were given a prescription for oral

penicillin and cloxacillin upon enrollment. Grayson et al. randomized 116 patients who presented with moderate to severe cellulitis to 2 g intravenous cefazolin and 1 g probenecid orally or 1 g intravenous ceftriaxone and placebo [36]. Clinical cure rates were similar: 86% in the cefazolin arm versus 96% in the ceftriaxone arm ($P = 0.11$) and remained equivalent up to 1 month of follow up, 96% versus 91% ($P = 0.55$). Both studies excluded patients with penicillin allergies, septic patients requiring hospitalization, patients with evidence of osteomyelitis, and significant renal failure.

Oral antibiotics with a broad spectrum of antimicrobial activity and equivalent bioavailability to intravenous regimens offer another alternative for the outpatient management of patients with complicated skin and soft-tissue infections. In a randomized trial comparing intravenous or oral levofloxacin and intravenous ticarcillin/clavulanate alone or followed by oral amoxicillin/clavulanate, 44 of 200 patients in the levofloxacin group had oral therapy alone [25]. Forty patients (90·9%) in this subset had clinical cure, which was a similar rate to the overall responses: 84.1% in the levofloxacin group and 80.4% in the ticarcillin/clavulanate group. Although the subset receiving only oral levofloxacin was not specifically analyzed, the authors caution that it may have had less severe disease. The other fluoroquinolones, for example moxifloxacin, also with improved gram-positive activity, could be expected to be similarly effective.

There are many options for patients with more complicated cellulitis, and choice of antibiotic should be individualized based on the patient's history and any extenuating circumstances. For most patients, outpatient therapy is safe and effective. Once daily regimens such as cefazolin and probenecid provide an easy, effective, and low-cost alternative. Follow-up and clinical response should dictate changes of antibiotic therapy.

Furuncles and carbuncles

Furuncles or "boils" are infections of hair follicles usually caused by *S. aureus*. Typically lesions are painful, erythematous nodules with an overlying pustule. When several furuncles coalesce to form a larger abscess this is a carbuncle. Large furuncles and carbuncles need incision and drainage [7]. Warm compresses promote drainage and antibiotics are rarely required unless there are systemic symptoms or an extensive cellulitis [7].

Outbreaks can occur within families and individuals in close living quarters (e.g. in prisons). Sports teams, especially involving contact sports, can also experience outbreaks. Recurrent furunculosis seems to be associated with *S.aureus* nasal colonization [41]. The National Health and Nutrition Examination Survey (NHANES) demonstrated an overall colonization prevalence of *S. aureus* of 32.4% among non-institutionalized Americans, with the highest rates seen in people younger than 65 years and males [42]. Surveillance studies have demonstrated that approximately 20% of individuals are persistently colonized with one type of strain (persistent carriers), 60% carry *S. aureus* intermittently and the remainder are noncarriers [43]. Those most at risk for persistent colonization appear to express high avidity binding receptors for *S. aureus*, along with being at high risk of environmental exposure to *S. aureus* through poor living conditions due to poverty, homelessness, overcrowding, poor hygiene, hospitalization, residence in a long-term care facility, or incarceration [42,43].

Eradication with mupirocin [44] (applied to the nares for 5 days each month) or systemic treatment with low-dose clindamycin [45] (150 mg/day for 3 months) is effective in reducing recurrence rates of furunculosis.

Soft-tissue infections and MRSA infection

The majority of *S. aureus* strains still remain sensitive to cloxacillin, but MRSA strains causing infection continue to increase in prevalence, with country-specific prevalence rates as high as 50% in Japan, Eastern Europe, the Middle East and South America [46]. While MRSA infections were first reported in hospitalized patients in 1967, more recent reports have identified MRSA strains causing infection in community-dwelling individuals who have neither previous admission to hospitals nor risk factors for disease [47]. These infectious diseases syndromes have been classified as healthcare-associated (HA-MRSA) and community-associated MRSA (CA-MRSA), respectively. Currently, the most important clinical differentiating characteristics are their

phenotypic susceptibility patterns, with the majority of CA-MRSA still retaining sensitivity to trimethoprim-sulfamethoxazole, tetracyclines, and clindamycin [47]. Community isolates frequently contain genes for the virulence factor Panton-Valentine leukocidin [47].

The prevalence of MRSA colonization in the USA has been estimated to be 1.5% (95% CI 1.2–1.8), with 19.7% (95% CI 12.4–28.8%) of these MRSA strains being classified as CA-MRSA [48]. There are increasing reports implicating CA-MRSA as the leading cause of emergency room visits for SSTI in certain populations, especially in the young, minorities, intravenous drug users, men who have sex with men, military personnel, and inmates of correctional facilities [47]. Clinical and epidemiologic risk factors, however, cannot reliably distinguish between MRSA and methicillin-sensitive *S. aureus* [49].

Treatment outcomes for patients with mild to moderate CA-MRSA skin and soft-tissue infections are dependent on aggressive drainage of abscesses and less so on antibiotic therapy. In one randomized controlled trial conducted on patients with MRSA skin and soft-tissue infections, there was no difference in outcomes between patients receiving antibiotics compared to placebo when appropriate incision and debridement of abscesses was completed [50]. Other studies have confirmed that abscesses caused by MRSA can be cured with drainage alone [51,52]. However, in a large retrospective analysis of 492 patients with MRSA skin and soft-tissue infections, a significant increase in treatment failures (OR 2.80, 95% CI 1.26–6.22, $P = 0.01$) was demonstrated if initial therapy was with an ineffective agent [53]. These results were confirmed in another study of empirical therapy for community *S. aureus* infections which showed that use of an effective agent was associated with greater clinical resolution (OR 5.91, 95% CI 3.14–11.13) when controlled for incision, drainage and HIV status [54]. Guidelines for the management of CA-MRSA recommend for those patients with a mild to moderate SSTI in a high-risk population for CA-MRSA, empiric therapy consist of a 5- to 10-day course of an antibiotic effective against CA-MRSA (e.g., TMP-SMX, clindamycin, or doxycycline) [55–57]. Counseling regarding the importance of good hand hygiene and wound treatment is recommended in conjunction with treatment, in order to prevent the transmission of MRSA to close contacts and the recurrence of infection [55,57].

For those patients with more severe SSTI at high risk for CA-MRSA, it is recommended that empiric therapy with parenteral systemic antibiotic therapy be initiated, along with admission to hospital with appropriate contact precautions and drainage of abscesses [57]. Empiric therapy with vancomycin is currently the first-line choice, although parenteral formulations of TMP-SMX or clindamycin are acceptable alternatives [55]. Other alternatives to vancomycin include linezolid, tigecycline, daptomycin, or quinupristin-dalfopristin [56]. These alternatives to vancomycin should only be considered after consultation with an infectious diseases specialist because of their risk profiles and cost, and lack of familiarity of use among physicians.

Treatment to eradicate MRSA colonization is not routinely recommended for individual CA-MRSA infections [55,57]. In a cluster-randomized placebo-controlled trial of mupirocin in soldiers, there was no decrease in infections (difference in infection rate between placebo and mupirocin groups 0.2%, 95% CI −1.3 to 1.7%) and new colonization was not prevented, despite eradication of CA-MRSA in colonized participants [58]. Decolonization may be considered for those patients with recurrent CA-MRSA infections or where there is evidence of ongoing transmission, but optimal regimens have not been established [57].

Necrotizing fasciitis

Case presentation 2

A previously healthy carpenter presents to the Emergency Department with fever and a painful arm. Yesterday at work he began to notice a sore right shoulder, was assessed in the Emergency Department later that evening, and diagnosed with a soft-tissue injury. Today he has pain in his shoulder and upper arm as well as fever and lethargy. On examination he is in moderate to severe distress from the pain, his temperature is 38·9°C, heart rate 122 per minute, and blood pressure of 90/60 mmHg. There is no obvious trauma or rash on his arm, but it is generally swollen and exquisitely tender to palpation and on movement of the shoulder or elbow. You begin to wonder if this man has a life-threatening infection.

Necrotizing fasciitis involves infection of the subcutaneous tissue with rapid spread and destruction of skin, subcutaneous fat, and fascia. Fortunately, it is a relatively uncommon life- and limb-threatening infection, but requires early recognition, prompt surgical intervention, and appropriate antibiotics. Many names have been used based upon clinical circumstances and pathogen, for example classic (clostridial) gas gangrene, clostridial cellulitis, non-clostridial gas gangrene, Fournier gangrene, Meleney's synergistic gangrene, necrotizing cellulitis, crepitant cellulitis, streptococcal gangrene, and, in the lay press, the term "flesh-eating bacteria" has been coined. Classification systems have also been developed based on pathogen [10] but are unhelpful clinically.

The literature on necrotizing fasciitis is predominately empiric, based on retrospective reviews and small case series. With the emergence of group A streptococcal fasciitis and associated toxic shock syndrome, more knowledge and understanding has been gained, but because of the relative rarity of cases and the complexity of the illness, randomized trials of management will be difficult to undertake.

The incidence of necrotizing fasciitis has been estimated at four cases per million [59]. A prospective cohort study monitoring the incidence of group A streptococcus in Ontario, Canada between 1991 and 1995 showed an increasing incidence from 0·85 per million to 3·5 per million during the study [60]. The CDC has estimated 500 to 1500 cases of group A streptococcus worldwide annually [61].

The presentation of necrotizing fasciitis can vary from the appearances of a simple cellulitis or soft-tissue injury to the classic hemorrhagic bullae, presence of soft-tissue gas, septic shock, and multiorgan failure. Toxic shock syndrome and multiorgan failure were also present in 47% of patients with group A streptococcus necrotizing fasciitis [60]. Most cases of necrotizing fasciitis initially present with a cellulitis but progress over hours to days with spreading erythema and edema. Hemorrhagic bullae can form as a result of skin necrosis secondary to vessel thrombosis. Pain out of proportion to clinical findings is commonly reported as an important early sign. Anesthetic skin due to destruction of nerves can be a late sign. Soft-tissue gas is a classic finding especially with clostridial infection. Estimates of the frequency of these signs and symptoms are not available.

Necrotizing fasciitis should be considered in any patient with "cellulitis" and systemic symptoms of fever and tachycardia, or rapidly spreading infection. Commonly necrotizing fasciitis starts at a preexisting skin lesion, such as a surgical site, trauma, chronic skin problems (e.g., pressure ulcer, diabetic foot, ischemic ulcer, or psoriasis), and in children varicella infection predisposes to necrotizing fasciitis [10,59,60,62–65]. In Kaul et al. a predisposing skin lesion was present in 74% of cases of group A streptococcus necrotizing fasciitis [60]. Any underlying medical condition, such as diabetes, alcohol abuse, immunosuppressive illness or treatment, cardiac disease, peripheral vascular disease, chronic lung disease, or chronic renal failure, should increase the suspicion for necrotizing fasciitis [10,59,60,62,63,65]. In Kaul et al. one or more of these conditions were present in 71% of cases [60]. Any area of the body can be involved, but the lower extremity accounted for 53% of cases, while the upper extremity was involved 29% of the time [60].

Necrotizing fasciitis can be caused by many organisms and usually is polymicrobial with a mixture of aerobic and anaerobic bacteria. One review showed that 85% of confirmed cases of necrotizing fasciitis were polymicrobial, while *S. aureus*, *S. pyogenes*, and *Clostridium* spp. were the most commonly isolated single pathogen [66]. Usual aerobic pathogens are *S. aureus*, *S. pyogenes*, and *E. coli*, while *Clostridium* spp., *Bacteroides fragilis*, and *Peptostreptococcus* spp. are predominate anaerobes. Rarely, and usually as a co-pathogen, other gram-positive organisms such as *Streptococcus pneumoniae*, gram-negatives such as *Pseudomonas aeruginosa*, *Serratia*, *Vibrio*, *Proteus*, *Enterobacter*, *Pasteurella*, *Eikenella*, and *Neisseria* spp., and anaerobes *Fusobacterium* and *Prevotella* spp. can cause necrotizing fasciitis.

The gold standard for diagnosis is surgical exploration to determine fascial involvement and to provide material for culture and microscopic examination [10,59,62–65,67]. Surgical exploration will also indicate the need for surgical debridement. In a small retrospective study, a frozen-section biopsy with urgent histopathologic analysis reduced mortality [68]. Fine-needle aspirate is positive for bacteria or pus 80% of the time [69]. Soft-tissue gas observed clinically or with plain films is diagnostic, but not always present. Ultrasound, CT, and MRI have all been used to aid

in the diagnosis of necrotizing fasciitis [69–75] but performance indicators (sensitivity and specificity) of ultrasound and CT in diagnosing necrotizing fasciitis have not been published. In two studies, totalling 25 patients, MRI had a 100% sensitivity but the specificity ranged from 75% to 100% [73,74]. Other conditions (e.g., cellulitis and abscesses) can be indistinguishable from necrotizing fasciitis [75]. Imaging should not delay definitive surgical treatment in the unstable patient. Laboratory investigations such as creatinine kinase, C-reactive protein, serum sodium, white blood cell count, serum calcium, creatinine, urea, and coagulation profiles have all been proposed to aid diagnosis, but lack sensitivity to reliably rule out necrotizing fasciitis [10,59,60,76,77].

Case presentation 2 (continued)

As you page the surgeon and begin resuscitating this young man, you wonder which antibiotics you could give immediately to cover the potential pathogens and whether there are other therapies that might save his life.

Immediate resuscitation, including ventilatory and inotropic support, prompt surgical debridement or amputation, and broad-spectrum parenteral antibiotics are the mainstay of management [10,11,59,60, 62–65,67]. Owing to the diversity of potential pathogens and because the majority of cases of necrotizing fasciitis are associated with polymicrobial infection, the most commonly recommended initial antibiotic is a β-lactam/β-lactamase inhibitor plus clindamycin [10,11,39,62–65,67,78]. Acceptable alternative regimens include single agents such as carbapenems, second-generation cephalosporins or fluoroquinolones with anaerobic activity and combinations with ampicillin and metronidazole or clindamycin, with either a third-generation cephalosporin, an aminoglycoside, fluoroquinolone, or aztreonam [10,11,59,62–65,78]. With animal models of group A streptococcus necrotizing fasciitis, clindamycin has been shown to have more effective killing power than penicillin, because bacteria reach the stationary growth phase rapidly and penicillin loses effectiveness in this phase [79]. Clinical data seem to support this with improved survival in patients treated with clindamycin [60,78]. Also owing to its effect on protein synthesis inhibition and toxin production, clindamycin may improve survival in patients with group A streptococcus necrotizing fasciitis [10,60,62]. Once a pathogen(s) has been identified, antibiotics should be tailored to the pathogen(s). For group A streptococcus necrotizing fasciitis, penicillin and clindamycin is recommended [7,10,60,62]. In penicillin-allergic patients, a second- or third-generation (if *Pseudomonas* is a consideration) cephalosporin can usually be safely substituted [80,81]. If a patient has a true penicillin/cephalosporin allergy a fluoroquinolone, macrolide, or vancomycin may be alternatives.

In a case–control study intravenous immunoglobulin (IG) dosed at 2 g/kg appears to decrease mortality in patients with group A streptococcus necrotizing fasciitis [82], and in one small randomized trial mortality was 3.6 fold higher in the placebo group 4 deaths compared with the IG group 2 deaths although the results were not statistically significant [83]. All patients in these studies had toxic shock syndrome. Intravenous IG appears to modulate the superantigen response in group A streptococcus necrotizing fasciitis [60,82]. A conservative nonsurgical approach to group A streptococcus necrotizing fasciitis, using penicillin (4 million units every 6 hours), clindamycin (900 mg every 6 hours), and intravenous IG (2 g/kg) has been proposed. Seven successful cases (six with TSS) treated with this regimen have been reported [84]. Surgery was either not performed or only limited exploration was carried out. With the significant morbidity of large area debridement, this regimen potentially offers an alternative approach to group A streptococcus necrotizing fasciitis, but these preliminary data need further study, and currently an aggressive surgical approach remains an important component of management. Intravenous IG use in other forms of necrotizing fasciitis has not been studied and there is no evidence to support its use in these settings.

Hyperbaric oxygen therapy (HBO) has been used as an adjunct for necrotizing fasciitis. Multiple small, retrospective studies have been done in both clostridial and nonclostridial necrotizing fasciitis with variable results. A metaanalysis showed a significant reduction in mortality in both groups: 19% versus 45% in clostridial necrotizing fasciitis and 20·7% versus 43·5% in nonclostridial necrotizing fasciitis [85].

HBO should not delay surgical debridement and unstable patients should not be transferred, but this treatment modality should be used if available.

Mortality for necrotizing fasciitis is estimated to be around 40% [62]. Specifically group A streptococcus necrotizing fasciitis had an observed mortality of 34–43% [60,63]. Hypotension on presentation is associated with an 18-fold increase in death [60]. Age over 65, bacteremia, chronic illness, and multiorgan failure also were associated with increased mortality [60,86]. For a specific discussion of postoperative necrotizing fasciitis see Chapter 16, Infections in General Surgery.

Diabetic foot infections

Case presentation 3

A 63-year-old man with a longstanding history of type 2 diabetes, complicated by peripheral neuropathy and chronic renal insufficiency, presents with a 2-day history of increasing drainage from an ulcer on his right foot. Today redness and swelling in his foot was noted. On examination he is afebrile, with a normal heart rate and blood pressure. On his right foot, he has a 2 cm ulcer on the sole between the 1st and 2nd metatarsal heads, with swelling and erythema to the mid-foot dorsally. His blood sugar is 18 mmol/liter and his WBC count is normal. Knowing the difficult nature of diabetic foot infections, you wonder which antibiotic, oral or parenteral, outpatient or inpatient, and other therapies might help in treating this man.

Due to the triad of vascular insufficiency, peripheral neuropathy, and impaired immune function, foot ulceration and infection are common among diabetic patients. Foot infections are among the most common cause for hospital admission in such patients [86,87]. Osteomyelitis is present in an estimated 20% of complicated infections and diabetic foot infection accounts for 50% of lower extremity amputations [88–90]. In 1996, 86 000 lower extremity amputations were performed on diabetic patients in the USA [90]. Diabetic foot infections need a multidisciplinary team approach involving endocrinologist, podiatrist, wound care specialist, diabetic educators, plastic, orthopedic, and vascular surgeons, and infectious disease specialist for their care [91] but the treatment of many patients is not in line with current guidelines [92].

Usually diabetic foot infections occur in a preexisting ulcer and prior trauma is common [93]. Peripheral neuropathy is the greatest risk factor for foot ulcers and infection [94] and patients often have no complaints of pain. Patients will usually have discharge from the ulcer, erythema, swelling, and unexplained hyperglycemia but there is no evidence a "signs-and-symptoms" checklist is a useful method of identifying infection in chronic wounds [95]. If there is no draining ulcer but the foot is erythematous and swollen, a Charcot foot (diabetic neuroarthropathy) should be considered [96].

Diabetic foot infections can be classified into two groups:

- non-limb-threatening, which have <2 cm of surrounding erythema extending from the ulcer, not a full-thickness ulcer and no systemic signs of toxicity;
- limb-threatening, which have >2 cm of surrounding erythema, full-thickness ulcer, presence of an abscess or soft-tissue gas, rapid progression, and signs of systemic toxicity [86,96].

Two-thirds of patients with limb-threatening infections have no fever, chills or elevated white blood cell count [97].

Surface cultures from wounds are not useful for identifying infection in chronic wounds [95]. Curettage of the base following debridement, or aspiration from non-necrotic tissue, may yield more dependable results to identify the infecting pathogen(s) [86,96]. In non-limb-threatening infection, *S. aureus* and group B streptococcus are considered the major pathogens [97–100]. *Enterococcus* spp., gram-negatives and anaerobes are often cultured, but it is unclear if they are colonizers or pathogens [96,101]. In moderate to severe diabetic foot infections, gram-negatives such as *E. coli*, *Proteus* spp., *P. aeruginosa*, *Serratia* spp., and *Enterobacter* spp., and anaerobes, such as *Bacteroides* and *Peptostreptococcus* spp., are often isolated and usually considered pathogenic [86,96–105].

For non-limb-threatening infections, initial antimicrobial therapy can be directed towards *S. aureus* and streptococci, and a first-generation cephalosporin, for example, cefazolin, is an appropriate choice. In a randomized, prospective trial of non-limb-threatening diabetic foot infections, 56 outpatients received 2 weeks

of either oral cefalexin 500 mg four times a day or clindamycin 300 mg four times a day as an outpatient [98]. From curettage specimens, 89% yielded gram-positive organisms (42% as a sole pathogen), 36% gram-negatives and 13% anaerobes. After 2 weeks of therapy, 91% were cured or improved, while of the five failures, three went on to cure with another agent covering gram-positive organisms (clindamycin, ampicillin, or cloxacillin). One of the other treatment failures had polymicrobial growth and, despite parenteral antibiotics for 2 months, ultimately required a forefoot amputation.

For limb-threatening diabetic foot infections, broad-spectrum antibiotics are recommended and many of the trials of complicated or moderate to severe cellulitis included diabetic foot infections. Randomized trials specifically performed on diabetic foot infections included use of ampicillin/sulbactam [103,104], imipenem/cilastin [104], cefoxitin [99], ceftizoxime [105], ofloxacin [103], moxifloxacin [106], and ertapenem [107]. All the trials had similar results with clinical cure or improvement in the range of 80–90%. A systematic review concluded that the evidence was too weak to recommend any particular antimicrobial agent for foot ulcers in diabetes [108]. In certain circumstances, outpatient therapy would be appropriate depending on diabetic control, extent of infection, and availability of follow-up.

There are other interventions that can be used in the management of diabetic foot infections. The type of wound dressing is an underused tool and new technologies in skin substitutes have shown promise in chronic ulcers, but further research is required to support their use in diabetic foot infections [86,95,109]. A randomized controlled trial of negative pressure wound therapy for the treatment of diabetic foot ulcers reported greater ulcer closure with negative pressure therapy compared with moist wound dressings [110] but a systematic review that included all kinds of wounds found little evidence to support negative pressure therapy [111]. Non-weight-bearing and even rigid immobilization is often recommended, although no randomized trials have been performed [112–115]. Hyperbaric oxygenation has been shown to improve healing of chronic ulcers [116], is cost-effective when compared to standard care [117], and has been effective in several small studies in diabetic foot infections [118–120]. Urgent vascular bypass surgery can be an option if ischemia is a major contributor to a non-healing ulcer or infection. The risks of such surgery must be balanced with the expected benefit for each patient [121].

For a further discussion on the management of complicated infections and osteomyelitis in diabetic patients, refer to Chapter 3, Bone and Joint Infections.

Animal bites

Case presentation 4

A 59-year-old woman, who was trying to intervene in a fight between the family dog and a neighborhood dog, notices a 2 cm laceration over the 5th metacarpophalangeal joint after the squabble was broken up. She has a past history of angina and hypercholesterolemia and is unsure when her last tetanus booster was given. Both pets have been immunized annually. You wonder, should you close the laceration? Does she need prophylaxis and, if so, with which antibiotic? Should she receive treatment for rabies?

Animal bites are very common. The vast majority of people never seek medical attention. Dog bites account for 90% of all bites, cats (5%), humans (2%), rodents (2%), and all other animals less than 1% [122]. It is estimated than 4·5 million dog bites occur annually in the USA and 7·3–18 per 10 000 bites seek medical attention [123–125]. An estimated 10 000 hospitalizations and 20 deaths per year occur secondary to dog bites, most being in children [124,126]. Deaths are usually due to the attack itself and only rarely from secondary infectious complications. Most bites are from family pets and a minority from stray animals.

Patients with bites have a bimodal pattern of presentation. If children are bitten, if the injury is significant, or if there are concerns over the potential for infection, or for tetanus and rabies, medical attention is sought immediately. Later, patients will present with signs and symptoms of secondary infection. An estimated 3–18% of dog bites and 28–80% of cat bites become infected [127]. Most bites occur on the hand or arm, children are more likely to be bitten on the face, males are more likely to be bitten by a dog, and females more likely to be bitten by a cat [128].

Important historical information to focus on include the past medical history of the patient, especially any history of immunosuppression or significant chronic disease, status of tetanus immunization, time of and circumstances surrounding the event (provoked or unprovoked), and details concerning the animal, for example health, ownership, and location. Many patients will be reluctant to divulge information owing to concern over reprisal on the animal by local authorities. Many cities and regions have mandatory reporting of animal bites. The wound should be assessed for site and potential for nerve, tendon, bone, or joint involvement, especially on the hands and feet. Any wound over a metacarpophalangeal joint should be considered a clench fist injury (punch injury). If the patient presents with established infection, systemic signs, site and extent of infection, lymphadenopathy, and possibility of tenosynovitis, osteomyelitis and septic arthritis should be considered.

Copious irrigation, debridement of necrotic tissue, and removal of foreign bodies are essential in early management of bite wounds [126–128]. Puncture wounds should be irrigated with a needle or plastic tip catheter inserted into the wound. Infected wounds should be opened if previously sutured, eschar removed and abscesses drained, then irrigated copiously. Closure of bite wounds is controversial, as there are no randomized studies of this intervention. Wounds less than 24 hours old, with no signs of infection, on the face, trunk, or proximal extremities can probably be closed safely [127]. All wounds on hands or feet, should be left open, especially if caused by cat or human [126–128].

Talan et al. have examined the bacteriology of infected dog or cat bites [129]. They examined the pathogens responsible for 50 dog bites and 57 cat bites. There were a mean of five pathogens per wound with a range of 0–16. For dogs, the most common aerobic bacteria were *Pasteurella* spp. (50% of patients) especially *Pasteurella canis*, *Streptococcus* spp. (46%), *Staphylococcus* spp. (46%), *Neisseria* spp. (16%), and *Corynebacterium* spp. (12%), while the most frequent anaerobes were *Fusobacterium* spp. (32%), *Bacteroides* spp. (30%), *Porphyromonas* spp. (28%), and *Prevotella* spp. (28%). Cats had similar bacteria, with the exception that *Pasteurella* spp. grew in 75% of cases with *P. multocida* being the most frequent species. From these data, the authors recommended a β-lactam/β-lactamase inhibitor or a second-generation cephalosporin with anaerobic activity. The combination of clindamycin and a fluoroquinolone was also recommended. Treatment guidelines have been published [7], however there are no prospective trials nor comparative studies of different antibiotic regimens for treating infected animal bites.

In human bites, the usual organisms are *S. aureus*, *Streptococcus* spp., and anaerobes, as well as an organism specific to the oral flora of humans, a fastidious gram-negative rod, *Eikenella corrodens*. It has an unusual sensitivity profile in that it is sensitive to penicillin and β-lactam/β-lactamase inhibitors, but relatively resistant to cloxacillin, first-generation cephalosporins, erythromycin, and clindamycin [126]. A β lactam/β-lactamase inhibitor combination is an appropriate initial choice.

The majority of patients with infected bite wounds can be managed as outpatients with oral antibiotics. Alternatively, parenteral antibiotics could be initiated with stepdown to oral therapy when the infection is resolving. This can be accomplished on an out- or inpatient basis, depending on clinical circumstances.

Antibiotic prophylaxis of animal bites is controversial. A Cochrane Library systematic review showed a favorable odds ratio for prophylaxis of cat and human bites, but not dogs, and for prophylaxis in hand wounds, but not face/neck or trunk wounds [130]. A randomized, blinded, placebo-controlled trial of 185 patients with animal bites using amoxicillin/clavulanate for prophylaxis, showed no difference in wounds less than 9 hours old, but a significant difference in those 9–24 hours old [131]. Therefore the animal, location of wound, and time to presentation all seem to affect the risk of infection and need for prophylaxis.

Animal bites can potentially transmit rabies and many patients will seek medical attention for fear of rabies infection. This is a rare occurrence in industrialized countries. In Canada, 22 rabies cases have been reported in 56 years [128]. In the USA, 32 cases over 16 years have been reported [132]. Immunized animals who are acting normally over a period of 10 days are not rabid. In certain areas, wild animals such as bats, raccoons, skunks, and foxes have been rabid. Local public health authorities can be a valuable resource in ascertaining the risk of rabies transmission in an individual case and the need for post-exposure prophylaxis.

Infections of skin and underlying soft tissue are a common problem in primary care. While most infections are managed without complication, those referred to the hospitalist/consultant are often in patients who have failed therapy, have significant comorbidity, or have a life- or limb-threatening infection. A thorough understanding of both common and unusual infectious etiologies, and local resistance patterns, are important in guiding antimicrobial choices. As well, other interventions to improve outcome can be employed and should be considered as part of the management of patients.

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CHAPTER 3
Bone and joint infections

William J. Gillespie

Introduction

The evidence base for diagnosis and management of musculoskeletal infections has become stronger in the last 5 years with the publication of a number of systematic reviews and meta-analyses, and a substantial number of new primary trials. The use of likelihood ratios (LR) and diagnostic odds ratios (DOR) derived from meta-analysis of diagnostic studies should prove helpful in clinical practice. However meta-analysis of diagnostic studies is an emerging technique, subject to bias and variation in the included studies [1], and it is likely that there will be considerable refinement of the current methods in the next few years. Two important points should be kept in mind for the present. First, the performance of diagnostic tests which measure host inflammatory response may be misleading when their performance characteristics are applied to people with other disorders, particularly inflammatory polyarthritis. Second, the results of a sequence of tests using LRs derived in different contexts may also be misleading, particularly if the tests are not truly independent of each other [2]. This chapter considers three important examples of musculoskeletal infection: infectious arthritis in adults, prosthetic joint infection, and osteomyelitis in the diabetic foot.

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Infectious arthritis

Case presentation 1

A 76-year-old woman presents to her family practitioner with a 72-hour history of increasing pain in the left knee associated with fever and malaise. She has been unable to walk for 12 hours prior to presentation. She has a 5-year history of osteoarthritis progressively affecting both knees for which she had taken a number of different non-steroidal anti-inflammatory agents, until 4 months ago when her medication was changed to paracetamol 2 g daily on account of medication-associated gastrointestinal discomfort. She has had no surgery to the knee. There is no history of gout, injury, or other recent illness. Physical examination reveals a temperature of 39°C. The left knee is held in 30 degrees of flexion; any movement from that position is extremely uncomfortable. There is a tense and tender effusion in the knee, which is warm to the touch. The right knee is cool to the touch, without a palpable effusion. Examination of cardio-respiratory, gastrointestinal, and neurological systems is normal. Blood pressure is 140/95 mmHg. Initial laboratory tests have shown hemoglobin of 10.9 mg/dL, WCC of 15 000/μL with 85% PMN and an ESR of 86 mm per hour. Radiographic examination of the knee confirms the presence of osteoarthritis. Urinalysis is negative for sugar and protein. She is admitted to hospital for investigation of acute inflammatory arthritis of the left knee.

Background

Incidence/prevalence estimates for infectious arthritis have varied [3,4], depending on case definition and case mix. The incidence in people with rheumatoid arthritis is around ten times that in the general

population [3]. *Staphylococcus aureus* and streptococci remain the most frequent isolates in most reports. Other organisms may assume some importance in particular groups (e.g., tuberculous infection in immigrants from the developing world, and in people with HIV infection). The natural history of the untreated case is destruction of the infected joint. In adults, the case fatality rate may exceed 10% overall, and 25% in older people with rheumatoid arthritis [4].

Diagnosis of infectious arthritis

Clinical signs and laboratory studies

A recent systematic review [5] summarized current evidence for the predictive value of clinical signs, blood and synovial fluid analyses in the investigation of possible infectious arthritis. It found that:

1. Reported prevalence of infectious arthritis amongst patients presenting with acute monoarthritis to a specialist clinic is 8–27%.
2. Although the reference standard for confirming a diagnosis of infectious arthritis is a positive culture and Gram stain from examination of synovial fluid or tissue obtained by percutaneous needle aspiration, biopsy, or arthroscopy, the reference standard itself is imperfect. Therefore, the review included studies which had used positive Gram stain, positive aspirate or blood cultures, or response to antibiotics as a proxy reference standard.
3. A limitation of the current evidence is the lack of high-quality data in the included studies.
4. Clinical findings which characterize acute peripheral monoarticular arthritis do not predict infectious arthritis. The only clinical findings which occur in more than 50% of patients with infectious arthritis are joint pain (sensitivity 0.85; 95% CI 0.78–0.9), a history of joint swelling (sensitivity 0.78; 95% CI 0.71–0.85), and fever (sensitivity 0.57; 95% CI 0.52–0.62). Sweats (sensitivity, 0.27; 95% CI 0.20–0.34) and rigors (sensitivity, 0.19; 95% CI 0.15–0.24) are less common findings in infectious arthritis.
5. An abnormal peripheral WBC count (LR+ 1.4; 95% CI 1.1–1.8), ESR (LR+ 1.3; 95% CI 1.1–1.8), and CRP (LR+ 1.6; 95% CI 1.1–2.5) have poor diagnostic power for changing the pretest probability of infectious arthritis, mostly due to their low specificity. Nevertheless, blood culture may occasionally identify an organism even when culture of the aspirate fails.
6. In examination of a joint aspirate, WCC greater than 100 000 cells/μL has strong diagnostic power for infectious arthritis (LR+ 28.0, 95% CI 12.0–66.0; LR– 0.71, 95% CI 0.64–0.79); WCC greater than 50 000 cells/μL has moderate diagnostic power (LR+ 7.7, 95% CI 5.7–11.0; LR– 0.42, 95% CI 0.34–0.51). Differential WCC of greater than 90% PMN carries LR+ of 3.4 (95% CI 2.8–4.2) and LR– of 0.34 (95% CI 0.25–0.47).
7. Other synovial fluid evaluations (low glucose, protein >3 g/dL, and LDH >250 U/L) predict infection weakly or not at all.

Imaging

MRI has limited diagnostic power in diagnosing infectious arthritis in adults. Two studies, both with methodologic limitations, have reported the sensitivity and specificity of MRI signs in infectious arthritis [6,7]. For individual signs (95% confidence intervals unavailable), LR+ was 4.14 and LR− 0.08 for synovial enhancement [8]; LR+ 1.96 and LR− 0.42 for periarticular bone marrow edema; and LR+ 2.11 and LR− 0.34 for bone erosion [9]. These likelihood ratios may not be valid in people with inflammatory polyarthritis, as the same signs are characteristic of rheumatoid arthritis [10].

Microbial culture

Attempts to increase the yield of positive cultures in aspirates by better techniques of sampling and transport have been made. Immediate incubation of the aspirate in blood culture bottles appears to increase the rate of successful culture [11,12]. One study (54 participants) [13], using microbiologic culture as the reference standard, found that synovial biopsy (sensitivity 0.69; specificity 1.0) had better diagnostic performance characteristics than simple aspirate (sensitivity 0.31; specificity 0.97).

There is insufficient current evidence to confirm advantage of using the polymerase chain reaction (PCR) with broad-range bacterial primers in the diagnosis of inflammatory monoarthritis in the usual diagnostic laboratory setting [8,9,14].

Case presentation 1 (continued)

Initial results from the laboratory found WCC of 15 000/μL with 85% PMN and ESR of 86 mm per hour. Synovial fluid analysis indicates WCC of 65 000/μL, with 92% PMN. No organisms were identified on Gram stain.

The prevalence of infectious arthritis amongst all the cases of inflammatory monoarthritis seen in your unit in the last 5 years is 26%, providing a prior probability of infectious arthritis of 0.26, equivalent to pre-test odds of 0.35. Using the likelihood ratios from [5], Table 3.1 shows what happens to the probability of infection as the diagnostic information builds up.

Management

There is general agreement based on cumulative experience that the treatment of infectious arthritis requires both antimicrobial therapy and the removal by joint puncture and lavage, on a number of occasions if necessary, of the inflammatory exudate from the joint [4].

Antimicrobial therapy

Provisional (empiric) therapy should begin as soon as the results of synovial fluid microscopy are available, if these support the diagnosis. Until the results of culture become available (and if no culture becomes available) a "best guess" choice should be based on local prescribing guidelines, the patient's history and findings, the known local pattern of infecting organisms, and their likely sensitivity to antimicrobial agents.

Definitive choice of antimicrobial agent is determined by the sensitivity of the etiologic microorganism. Optimal duration of therapy is not known. A consensus benchmark for RCTs evaluating new antimicrobial agents was 2–3 weeks [15]. Initially in the acutely febrile patient, intravenous therapy has usually been preferred until the temperature has returned to normal, but there is no RCT evidence to support practice.

Aspiration and lavage

Both open joint drainage and arthroscopic drainage [16] appear effective. RCT evidence for the best method of joint aspiration/lavage is unavailable. Open drainage of the hip has been traditionally advised, but arthroscopic drainage/lavage techniques are becoming established for the hip also [17].

Corticosteroid therapy

A third proposed component of therapy [4], the administration of a short course of systemic corticosteroids, improved outcomes in an experimental model [18]. In a subsequent RCT in childhood infectious

Table 3.1 Diagnostic sequence for infectious arthritis

	Pre-test probability of sepsis	Pretest odds	Point likelihood ratio from test [5]	Post-test odds	Post-test probability of sepsis
Patient has acute monoarthritis					0.26
History: prior osteoarthritis; no other obvious risk factor	0.26	0.35	1	0.35	0.26
Physical examination: fever	0.26	0.35	0.67	0.24	0.19
Blood white cell count: >15 000 cells/μL	0.19	0.24	1.40	0.33	0.25
ESR: 85 mm/h	0.25	0.33	1.30	0.43	0.30
Synovial fluid WCC: 65 000cells/μL	0.30	0.43	7.70	3.30	0.77
Synovial fluid PMN: 92%	0.77	3.30	3.40	11.22	0.92

Note that it is the likelihood ratios from synovial fluid analysis which raise the probability of infectious arthritis from a low figure based on the frequency of infectious arthritis amongst cases of acute monoarthritis, to a level of probability which supports beginning presumptive therapy for infectious arthritis. A sensitivity analysis using the less favorable confidence limits from reference [5] raises the probability to 0.74; using the more favorable (upper) confidence limit, the probability of infectious arthritis is 0.98.

arthritis [19] a short course of dexamethasone was associated with reduced residual joint dysfunction and shortened the duration of symptoms. However its use in adults has not been reported. Given the increased risk of developing infectious arthritis associated with corticosteroid therapy of polyarthritis [20], caution is understandable at this point.

Implications for practice

In diagnosing infection in adults presenting with acute monoarthritis:

- Clinical findings and blood tests have poor diagnostic power.
- MRI has limited diagnostic power in diagnosing infectious arthritis in adults. It can distinguish anatomic and pathologic detail with great accuracy, but the signs in infection are also found in other inflammatory arthropathies.
- WCC greater than 100 000 cells/μL has strong diagnostic power, WCC greater than 50 000 cells/μL has moderate diagnostic power, and differential count of greater than 90% PMN has weak diagnostic power.

Implications for research

- The performance of diagnostic tests for infection which measure host inflammatory response should be evaluated in cohorts of people with suspected infection and inflammatory polyarthritis.
- The use of corticosteroids in adult septic arthritis, already used in some clinics, should be examined in carefully designed RCTs before wider adoption.

Prosthetic joint infection

Case presentation 2

A 67-year-old woman with a 14-year history of rheumatoid arthritis presents with a 1-year history of increasing discomfort in the right hip. Three years previously she had developed an acute postoperative infection following a primary elective right total hip replacement for which she had been treated by debridement, suction drainage and irrigation, and antimicrobial therapy. Recently, although she has been generally well with satisfactory control of her rheumatoid arthritis, pain in the right hip has recurred and radiographs show loosening of the implant.

Background

Although the incidence is low, prosthetic joint infections (PJI) result in substantial patient morbidity, loss of function, reduced quality of life, and societal costs. Clinical presentations range from an acute illness with local and systemic symptoms (characteristic in early postoperative and hematogenous infections), to low-grade infection leading to insidious prosthetic loosening and pain. PJI is hard to eradicate due to formation of surface biofilms on implant materials [21–23].

The incidence of infection after primary hip arthroplasty has decreased since the late 1960s, when infection rates were as high as 10% [24]. The introduction of antimicrobial prophylaxis and the development of techniques to reduce the burden of airborne bacteria in the operating room led to infection rates under 2% by the 1990s [25,26]. The increasing incidence of MRSA has raised the question of whether antibiotic prophylaxis should now include a glycopeptide, but there is insufficient current evidence to determine a threshold prevalence of MRSA at which switching to glycopeptide prophylaxis might be cost-effective [27].

Estimates of incidence of PJI derived from case series, surveillance programs, and national arthroplasty registers are susceptible to bias, due to differing diagnostic criteria for infection and operative risk case mix. Accepting that limitation, in the decade 1998–2007 [28–34] the incidence of any surgical site infection occurring within 1 year appears, overall, under 2%. Less than half of incident infections occur by 3 months. The ratio of superficial to deep SSIs in the first 3 months is approximately 3:1. By 2 years, up to 0.5% of primary total hip replacements will have had a reoperation for deep infection.

Diagnosis of prosthetic joint infection

The reference standard

There is no "gold standard" definition of prosthetic infection. Most investigators have identified a proportion of cases (10–15%) with convincing clinical evidence of infection from which it has not been possible to culture an organism. As a result, some reliance on assessing the host inflammatory response, a surrogate for infection, has been adopted in clinical practice. This is somewhat problematic for diagnosing infection in people with inflammatory polyarthritis. Neutrophils

are prominent in the histology and cytology of rheumatoid arthritis [35,36]. Investigators have frequently excluded patients with inflammatory polyarthritis from studies of blood indicators, aspiration specimens, and histologic findings suggestive of inflammation. Where they have been included, subgroup information has rarely been provided.

In clinical practice, the Mayo Clinic definition [25] or a modification of it [37] has been used as a working definition. It requires the presence of at least one of four criteria – growth of the same microorganism in two or more cultures from preoperative aspirates or from intraoperative specimens; purulence of synovial fluid from an aspirate or at the implant site; presence of granulocytes on histopathologic examination of periprosthetic tissue; or presence of a sinus tract communicating with the device.

Preoperative tests

Blood investigations

In studies in people without inflammatory polyarthritis, three inexpensive blood tests have good predictive capability for supporting or ruling out a suspected PJI. Each pair of LRs (positive and negative), based on a single study only, are: ESR >30 mm/h [38] (LR+ 5.47, LR− 0.18); CRP >10 mg/L [38] (LR+ 12.0, LR− 0.08); and IL-6 >10 ng/L [39] (LR+ 20, LR+ 0.05).

Imaging

In a metaanalysis of anti-granulocyte scintigraphy [40], LR+ was 3.99 (95% CI 3.13–5.09) and LR− was 0.22 (95% CI 0.15–0.34) The data on FDG PET, although scanty, suggest that it may be a more powerful examination. One metaanalysis [41] calculated LR+ of 9.58 and LR− of 0.08. More recent data from a single center [42] indicated LR+ of 13.6 and LR− of 0.05.

Aspiration of the hip

No systematic review of the diagnostic performance of preoperative aspiration and culture has been identified. In reports from single units since the early 1990s, sensitivity has ranged from 0.12 to 0.86, and specificity from 0.81 to 1.00. A recent report [43] includes a short narrative review.

Intraoperative tests

Histology

Histologic examination may be unreliable in patients with inflammatory joint disease [44]. Variation in the quantitative criteria for making an intraoperative frozen section diagnosis of infection from histologic examination is reflected in the wide range of reports of sensitivity (0.18 to 1.00) and specificity (0.64 to 1.00) [45–55]. No systematic review of these reports is currently available. While a positive Gram stain in a tissue sample does predict infection, it has poor sensitivity (0.06) compared with a positive culture result from the same sample used as the reference standard [44,56]. Its sensitivity compared with a positive histology result as reference standard is also poor (0.12).

Microbial culture of fluid or tissue specimens

Isolation of the same organism from three or more of at least five independent tissue specimens is highly predictive of infection (LR+ 169) [44]. A single positive culture is less convincing (LR+ 4.3).

Laboratory culture of material from a possible prosthetic infection should include a careful search for small colony variants (SCVs) which contribute to the resistance to treatment of biofilm-associated infections [22,23].

Sonication of removed prostheses

Submission of the explanted implant to the laboratory, under a strict protocol, for low-energy ultrasonication appears promising. One study [57] found that sonicate fluid culture had significantly better sensitivity (0.78) than two or more positive periprosthetic-tissue cultures (0.60). Specificities for both were 0.99.

Molecular diagnosis using polymerase chain reaction

Three studies have compared the performance characteristics of polymerase chain reaction (PCR) compared with culture in PJI [58–61] and others have included material from PJI which is not reported separately. The place of PCR in the diagnosis of PJI is currently unclear.

Case presentation 2 (continued)

Recurrence of surgically acquired infection is clearly possible. The implant is no longer stable, and the condition of the soft tissues at the operative site is categorized as showing evidence of moderate damage, not surprising given the past history of two procedures, the second of which had required extensive debridement.

Following discussion she expresses her wish to consider two-stage revision arthroplasty, and asks what diagnostic tests would help to support or exclude a diagnosis of persisting infection.

The fact that she has rheumatoid arthritis means that the majority of tests in the diagnostic sequence which would normally be undertaken during preoperative evaluation to firm up a diagnosis of recurrent infection may be of limited value since the published likelihood ratios will not necessarily be reliable. Intraoperative culture will be the pivotal investigation in her case. The circumstances in this case led to advice that operative cover with intravenous (IV) vancomycin should be commenced during surgery as soon as the tissue specimens for the laboratory had been secured.

Treatment and outcomes

Programs for cure or remission of infection, and restoration of good function after PJI have developed empirically, almost completely without support of evidence from RCTs. A management algorithm which reflects most contemporary practice illustrates how the choice of management program for individual patients may be made [62].

For a small number of people with PJI, restoration of good function may not be achievable. They may be offered removal of the prosthesis alone, or long-term suppressive antimicrobial therapy.

For the great majority, one of three approaches to the management of PJI offer odds of better than 4 to 1 of an acceptable functional outcome without recurrence of infection.

People in whom infection occurs early after implantation, or who have a late hematogenous infection, may be offered debridement of soft tissues involved in the infection, with retention of the implant and a period of antimicrobial therapy of at least 3 months [37]. Criteria for implant retention are: (1) a stable implant; (2) a pathogen with susceptibility to antimicrobial agents active against surface-adhering microorganisms; (3) absence of a sinus tract or an abscess; and (4) duration of symptoms of infection of less than 3 weeks. Debridement and retention applied using these patient selection criteria achieved greater than 80% recurrence-free function at 2 years. A preferred antimicrobial therapy regimen for debridement/retention in hip PJI caused by methicillin-susceptible *S. aureus*, based on the results of one RCT [63], has used intravenous rifampin plus (flu)cloxacillin for 2 weeks, followed by rifampin plus ciprofloxacin or levofloxacin for 3 months.

People with PJI who do not meet these criteria are likely to be offered a further operative procedure which aims to remove the infected prosthesis, eradicate infection, and insert a new prosthesis by either one-stage or two-stage exchange arthroplasty. Delivery of antimicrobial agents, an essential component of each option, may be achieved parenterally, orally, or by the use of antibiotic-loaded bone cement (ALBC).

A comprehensive narrative review [64] of data from 1641 patients treated for PJI from 29 centers in a number of countries confirmed that two-stage exchange was associated with successful outcome with (93%) or without (86%) the use of ALBC. One-stage exchange had similar success if ALBC was used, but poorer outcome (59% success rate) if it was not. A recent report of two-stage exchange procedure with ALBC, but without the use of a prolonged course of antibiotic therapy, achieved minimum recurrence-free period of 2 years in 85% of patients [65].

Case presentation 2 (continued)

This patient agreed to advice that a two-stage exchange arthroplasty was indicated. At surgery, no fluid collection was found, and seven tissue specimens were submitted for intraoperative histology and culture. Sonication of the prosthesis was unavailable. The first stage of a two-stage arthroplasty was completed and irrigation and suction drainage initiated. After 5 days of incubation, four of seven submitted periprosthetic tissue specimens grew a small colony variant of *S. aureus*, resistant to methicillin and ciprofloxacin, and sensitive to vancomycin, rifampin, fusidic acid, and cotrimoxazole. At that point IV rifampin was added to vancomycin, and continued until day 14, when IV therapy was discontinued and oral rifampin/

continued

Case presentation 2 (continued)

cotrimoxazole therapy administered until the second stage of the two-stage exchange arthroplasty was carried out, 8 weeks following the first stage. Over the procedure, IV vancomycin was administered as surgical prophylaxis and oral rifampin/cotrimoxazole was continued for a further 3 months.

Implications for practice

In the prevention, diagnosis, and management of PJI:

- There is insufficient current evidence to determine a threshold prevalence of MRSA at which switching to glycopeptide antibiotic prophylaxis for prosthetic joint surgery might be cost-effective.
- Preoperative blood tests (ESR, CRP, IL-6) appear to be good and inexpensive screening tests in people who do not have inflammatory polyarthritis. Their diagnostic performance characteristics in people with inflammatory polyarthritis are unclear.
- Anti-granulocyte scintigraphy using monoclonal antibodies and FDG PET have good diagnostic performance characteristics in people who do not have inflammatory polyarthritis.
- Identification of PMN in preoperative aspirates or in operative tissue specimens has good diagnostic performance characteristics in people with suspected PJI who do not have inflammatory polyarthritis.
- The isolation of the same organism from culture of three or more independent operative tissue specimens in people with suspected PJI is highly predictive of infection.
- The diagnostic performance characteristics of molecular methods when compared with culture from operative tissue specimens in PJI remain unclear. Current reports show considerable heterogeneity.

Implications for research

- Further primary studies and metaanalyses of the performance of diagnostic tests used in suspected PJI should be conducted, particularly in people who have inflammatory polyarthritis.
- Although PJI affects only a small proportion of people who have undergone joint arthroplasty, and effective methods of management are available, innovative management regimens should in future be examined in large multicenter randomized trials.

Osteomyelitis in the diabetic foot

Case presentation 3

A 62-year-old man presents to his family practitioner with an infection in his left forefoot. He gives a history of type 2 diabetes mellitus of 8 years' duration, managed with oral hypoglycemic agents and diet. He is a non-(never) smoker, with a daily alcohol intake of 1–2 units. He appears systemically well; his metabolic control is adequate. Clinical examination of the foot demonstrates ulceration on the plantar surface of the foot under the 4th and 5th metatarsal heads, with a purulent discharge. Tendon, and possibly bone, are visible in the base of the ulcer. Cellulitis extends proximally above the ankle. His family practitioner refers him for further evaluation to the local multidisciplinary diabetes clinic.

Background

Incidence and prevalence

Foot ulceration is the major predisposing factor in diabetic foot infections. Approximately 15% of over 150 million people worldwide with diabetes mellitus will develop foot ulceration at some time in their life [66]. Estimates of incidence derived from cohort studies have varied depending on case mix, from 11 to 65 per 1000 person-years [67–71]. Over 50% of foot ulcers may become infected [70]. Annual incidence of infection in a clinic population with foot ulcers has been estimated at 5–9% [70,71].

Pathology and microbiology

Although a penetrating injury may implant pathogens directly into bone, contiguous soft-tissue infection preceded by skin ulceration accounts for most cases of osteomyelitis in the feet of diabetic patients. Devascularization of areas of bone may create a favorable environment for the establishment of biofilm-associated infection [21–23] with its associated resistance to antimicrobial therapy. Thus, surgical debridement of the infected bone remains an essential component of successful control of osteomyelitis in most cases.

Aerobic gram-positive cocci (particularly *S. aureus,* but also coagulase negative staphylococci and group B streptococci) are found in the majority of cases of osteomyelitis in the diabetic foot. Many isolates are methicillin-resistant [72]. Polymicrobial infections

are more common in chronic ulcers, and in people who have recently received antimicrobial therapy [73].

Classification schemes for diabetic foot ulcers have evolved over the last 25 years. The widely used Wagner Scale [74] is based on clinical impression of the pathologic anatomy. The University of Texas (UT) Classification [75,76] (Table 3.2) may be a better predictor of clinical outcome, as it takes into account the presence of both infection and ischemia. The International Working Group on the Diabetic Foot (IWGDF) diabetic foot risk classification, based on both anatomic and physiologic features, initially validated in 2001, is predictive of the risk of both ulceration and of amputation [77]. An update has recently been proposed [78].

Risk factors for infection and amputation in the presence of ulceration

Factors in the clinical presentation of a diabetic foot ulcer which are significantly associated with infection have been evaluated in a large cohort study [79], using multivariate analysis. These factors, with risk ratios (RR), were:

- wound depth to bone RR 6.7 (2.3–19.9)
- wound duration ≥ 30 days RR 4.7 (1.6–13.4)
- recurrent foot wound RR 2.4 (1.3–4.5)
- traumatic wound etiology RR 2.4 (1.1–5.0)
- peripheral vascular disease RR 1.9 (1.0–3.6).

The Infectious Diseases Society of America (IDSA) and IWGDF have collaborated in developing a classification scheme for infection severity which predicts the likelihood of amputation in the presence of a foot ulcer in a patient with diabetes (see Table 3.3). Validation of this classification was reported in 2007 [80].

Case presentation 3 (continued)

Physical examination at the diabetic foot clinic provides further information. He has mild retinopathy. Both popliteal pulses are palpable. No pulses are palpable in either leg below the knee. Blunt probing of the ulcer contacts bone. Both feet show intrinsic (hammer toe) deformities and are insensitive to the 5·07 Semmes–Weinstein filament test. Plain radiographs demonstrate soft-tissue swelling and loss of definition of tissue planes, and zonal osteopenia in the heads of both 4th and 5th metatarsals. These appearances are consistent with osteomyelitis.

This patient's history and findings appear consistent with a moderate infection (UT B3, IDSA/IWGDF grade 3). Further investigations are begun to establish the extent of the infection in his foot, and in particular to gain anatomic detail of the apparent involvement of the 4th and 5th metatarsals.

Principles of diagnosis and management

The principles of diagnosis and management of diabetic foot infections are set out in an evidence-based guideline [81] published in 2004. Although the evidence base for some of its recommendations has been strengthened by the subsequent publication of metaanalyses, and by some new primary studies, they continue to represent best practice.

Table 3.2 University of Texas Foot Ulcer Classification [75]

Wound grade	Stage 0	Stage 1	Stage 2	Stage 3
A Clean wounds	Pre- or post-ulcerative site that has healed	Superficial wound not involving tendon, capsule, or bone	Wound penetrating to tendon or capsule	Wound penetrating bone or joint
B Non-ischemic infected wounds	Pre- or post-ulcerative site that has healed	Superficial wound not involving tendon, capsule, or bone	Wound penetrating to tendon or capsule	Wound penetrating bone or joint
C Ischemic non-infected wounds	Pre- or post-ulcerative site that has healed	Superficial wound not involving tendon, capsule, or bone	Wound penetrating to tendon or capsule	Wound penetrating bone or joint
D Ischemic infected wounds	Pre- or post-ulcerative site that has healed	Superficial wound not involving tendon, capsule, or bone	Wound penetrating to tendon or capsule	Wound penetrating bone or joint

Table 3.3 Diabetic foot infection classification schemes [80]

Clinical findings	Infectious Diseases Society of America Classification	International Working Group on the Diabetic Foot Classification
Wound without purulence or any manifestations of inflammation	Uninfected	Grade 1
Manifestations of inflammation (purulence or erythema, pain, tenderness, warmth, or induration); any cellulitis or erythema extends ≤2 cm around ulcer, and infection is limited to skin or superficial subcutaneous tissues; no local complications or systemic illness	Mild infection	Grade 2
Infection in a patient who is systemically well and metabolically stable but has more than one of the following – cellulitis extending ≥2 cm; lymphangitis; spread beneath fascia; deep tissue abscess; gangrene; muscle, tendon, joint, or bone involvement	Moderate Infection	Grade 3
Infection in a patient with systemic toxicity or metabolic instability (e.g., fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, hyperglycemia, or azotemia)	Severe infection	Grade 4

Diagnosis of osteomyelitis

As in the diagnosis of prosthetic joint infections, establishing a single clinically useful diagnostic reference standard for osteomyelitis in the diabetic foot is somewhat problematic. The interpretation of microbial culture results may be complex or misleading due to prior antimicrobial therapy, polymicrobial infection, and superficial wound contamination. For these reasons, positive culture or positive histology from a bone biopsy is generally accepted as the reference standard for evaluating diagnostic tests.

Clinical findings

A positive probe-to-bone test provides moderate diagnostic evidence of osteomyelitis. One systematic review [82] (21 included studies, 403 participants) found summary LR+ 6.4 (95% CI 3.6–11.0). A negative test has a summary LR of 0.39 (95% CI 0.20–0.76).

Physician's assessment of the ulcer as Wagner Grade >2 provides moderate diagnostic evidence of osteomyelitis [82]. More evidence is required, as this finding is derived from two small studies (total of 43 participants) which reported LR+ of 3.9 (95% CI 0.96–16) [83] and 13 (95% CI 0.82–203) [84].

One study (35 participants) [85] reported that physician's "clinical judgment" predicted LR + of 9.2 (0.57–147) and LR- of 0.70 (0.53–0.92).

Blood investigations

An ESR above 70 mm/h in the context of a diabetic ulcer supports a diagnosis of osteomyelitis. An ESR of less than 70 mm/h does not rule it out. One systematic review [82] presented data from two studies (64 participants) [85,86]. ESR ≥70 mm/h had summary LR+ of 11.0 (95% CI 1.6–79) and LR− of 0.34 (95% CI 0.06–1.9).

The sensitivity of an elevated white blood cell count for a diagnosis of osteomyelitis was evaluated in one small study [87], which found poor sensitivity regardless of the cut-off used [82], and provided no data to calculate specificity.

Microbiological investigations

Superficial swabs from an ulcer or curettage from its edges and base are poor predictors of osteomyelitis, and of the microbial isolates from bone biopsy. One study with 16 participants [88], found that culture of soft tissue obtained by curettage of the edges and base of an ulcer was a poor predictor of osteomyelitis confirmed by histological examination of a debridement bone specimen (LR+ 1.0, 95% CI 0.65–1.5; LR– 1.0, 95% CI 0.08–13).

Four studies [89–92] compared the microbiologic isolate from a superficial swab with the isolate from a deep tissue biopsy. All used slightly different methods which are summarized in Table 3.4.

Table 3.4 Studies comparing sampling techniques for diagnosis of diabetic foot osteomyelitis

Study	n	Index test	Reference Standard	Diagnostic performance of index test
Bill 2001 [89]	38	Superficial swab	Punch biopsy ulcer base, immediately following swab	Sensitivity 0.79, specificity 0.6, LR+ 1.96, LR− 0.36
Slater 2004 [90]	60	Superficial swab	Deep soft-tissue or bone sample at the junction of nonviable and viable tissue at debridement immediately following swab	Sensitivity 0.62*
Senneville 2006 [91]	69	Superficial swab	Percutaneous bone biopsy within 72 h of swab	Sensitivity 0.17*
Kessler 2006 [92]	21	Superficial swab	Percutaneous needle to bone surface immediately after swab	Sensitivity 0.19*

*Sensitivity calculated using number of superficial swab isolates identical to deep tissue isolates.

Preliminary data on the use of miniaturized oligonucleotide arrays [93] to differentiate colonized from infected wounds in <1 day found that genes for both virulence and resistance factors were present significantly more often in clinically infected wounds. The implications of this new technique in clinical practice remain to be established.

Plain radiographs

Plain radiographs have weak predictive value in the diagnosis of lower extremity osteomyelitis in people with diabetes. Nevertheless, they are inexpensive, easily obtained in most healthcare facilities, and provide useful clinical and anatomic information. One systematic review [82] reported a metaanalysis (7 studies; 217 participants). Summary LR+ was 2.3 (95% CI 1.56–3.3) and LR− was 0.63 (95% CI 0.51–0.78).

Limited specificity may be explained, first, by the observation that the bone changes of established osteomyelitis may also be seen in neuropathic bone and joint disease without infection. Contributing to limited sensitivity is the delay between onset of osteomyelitis and the onset of radiologic signs, typically 7–14 days.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) has moderate predictive value in the diagnosis of foot osteomyelitis, but if changes indicating osteomyelitis have been seen on plain radiographs, it may not always be necessary [94]. Eleven of 16 studies in one systematic review [95] included predominantly diabetic patients, and in six, all participants had ulceration. Summary LR+ was 3.8 (95% CI 2.5–5.8) and LR− 0.14 (95% CI 0.08–0.26). A particular advantage of MRI is the excellent anatomic detail of the extent of infection in bone, which facilitates surgical planning.

Nuclear imaging

The diagnostic accuracy of ^{99m}Tc bone scanning, indium scanning, and WBC imaging techniques is inferior to that of MRI in head-to-head comparison. One systematic review [95] found that MRI was markedly superior (DOR 149.9; 95% CI 54.6–411.3) compared with bone scan (DOR 3.6; 95% CI 1.0–13.3) At the 90% sensitivity cut point, the specificity for MRI was 0.98 compared with 0.29 for technetium. In 9 studies that compared plain radiography with MRI, MRI outperformed plain radiography (DOR 81.5; 95% CI 14.2–466.1 compared with DOR 3.3; 95% CI 2.2–5.0). In three studies comparing MRI with white blood cell (WBC) labeling, DOR for MRI was 120.3 (95% CI 61.8–234.3) compared with 3.4 (95% CI 0.2–62.2) for WBC studies. Another systematic review [96] found that ^{99m}Tc bone scanning, indium scanning, and WBC imaging techniques lacked useful specificity (range 0.62–0.89) in the diagnosis of infection in the diabetic foot.

Three studies [97–99] have compared MRI and FDG PET in people with diabetic foot disorders. FDG PET appears to distinguish between neuropathic

osteoarticular changes and osteomyelitis, but a clear picture of the cost-effectiveness of FDG PET compared with MRI awaits further comparative data.

Clinical presentation 3 (continued)

The clinical and radiologic evidence so far indicates that there is an open ulcer, a cellulitis, and a probable osteomyelitis, based on the positive probe-to-bone test and the plain radiographs. MRI shows reduced marrow signal intensity in T1-weighted sequences, and increased signal on fat-suppressed T2-weighted sequences in both 4th and 5th metatarsals, confined to the metatarsal heads and the distal third of each shaft. Soft tissue edema surrounds both 4th and 5th metatarsal heads, and cortical destruction is present on the plantar aspect of the shaft of the 4th metatarsal. Image-guided percutaneous biopsy from a dorsal approach using a 10 gauge Craig needle sampled both metatarsal heads.

As local community-acquired MRSA prevalence has been low, and the patient had no obvious MRSA risk factors, empiric antimicrobial therapy with cefalexin was commenced immediately after biopsy, and a formal surgical debridement planned for 72 hours later.

Although this patient had not been considered at high risk for MRSA, both samples grew a pure culture of MRSA susceptible to vancomycin, linezolid, daptomycin, doxycycline ($MIC_{90} \leq 2\,\mu g/mL$), trimethoprim-sulfamethoxazole ($MIC_{90} \leq 0.5/9.5\,\mu g/mL$) but resistant to clindamycin ($MIC_{90} > 8\,\mu g/mL$). No anaerobes were identified. The histologic appearances were those of osteomyelitis. Antimicrobial therapy was changed to vancomycin and trimethoprim-sulfamethoxazole when the cultures were received.

Treatment and outcomes

Surgical management

Based on long collective experience, but no RCTs, surgery continues to be a normal component of the management of osteomyelitis in the diabetic foot. Accordingly, surgical management follows the general principles of surgical management of osteomyelitis – resection of necrotic bone and soft tissue, management of the post-resection defect, and wound closure. The use of flaps to manage defects after forefoot surgery may be indicated in younger patients. In older patients, most surgeons have felt it appropriate to avoid primary skin closure, even where it seems technically possible, preferring delayed primary or secondary closure.

A review of the outcome of predominantly medical therapy for foot osteomyelitis (11 case series, 546 patients) [100] found remission rates of 25% to 91%. In a recent retrospective report of nonsurgical management from nine diabetes clinics (50 patients) [101], the remission rate was 64%. These reports raise the hypothesis that there may be a subset of diabetics with foot osteomyelitis who can be effectively managed in this way.

Choice of antimicrobial agent

A systematic review of primary studies published up to November 2002 found 23 RCTs evaluating the effectiveness or cost-effectiveness of antimicrobial agents in the treatment of diabetic foot infections [102]. Eight of these studies were double blind. The review, unsurprisingly in view of the heterogeneity of study participants, agents, pathogens, and outcome measures, found no evidence of the superiority of any particular intravenous or oral antibiotic regimen over any other. Metaanalysis was not conducted.

The clinical relevance of a systematic review with such a broad scope is limited; a more appropriate scope might be antibiotic X versus antibiotic Y in the treatment of infection with isolate pattern Z. But that presupposes that all primary studies also ask clinically useful questions formulated in this manner. However, the reviewers made some very pertinent observations. The quality of many of the trials was poor, particularly in respect of allocation concealment and blinding. The authors found little agreement on what is the key outcome measure for assessing the effectiveness of an antimicrobial in the management of diabetic foot ulcers. No trials reported the impact of interventions on health-related quality of life or on the development of antibiotic resistance. These are challenges for the pharmaceutical industry and the research community to consider.

Empiric preliminary antimicrobial therapy should be based on the likely microbial etiology and the current local antimicrobial prescribing policy. If an infection is severe (IDSA/IWGDF grade 4) current guidelines [81] recommend the use of broad-spectrum agents, but in mild to moderate infection,

therapy against gram-positive cocci may be sufficient. Isolation of MRSA from community-acquired infections appears to be increasing [73] and antimicrobial prescribing policies may need to take that into account.

Duration of antimicrobial therapy

Optimum duration of antimicrobial therapy has not been established using RCTs. Recommended duration of antibacterial therapy [81] ranges from 1 to 4 weeks for soft tissue infection, to >6 weeks if the complete resection of the infected bone is not achieved. If resection is complete (e.g., amputation of a toe with infection involving the middle phalanx and distal interphalangeal joint), and wound healing is proceeding satisfactorily, a shorter period is often sufficient.

General supportive management

The fundamentals of good diabetic foot care continue to apply during treatment of a diabetic foot infection, and the search for optimum wound dressing constitutes an area of active research. Both are beyond the scope of this chapter.

Adjuvant therapy: G-CSF

A recent systematic review [103] concluded that administration of G-CSF therapy does not appear to hasten the clinical resolution of diabetic foot infection or ulceration but is associated with a reduced rate of amputation and other surgical procedures. However, neither of the two included RCTs which recruited mainly participants with osteomyelitis [104,105] had power to demonstrate any significant effect for these outcomes.

Adjuvant therapy: hyperbaric oxygen therapy

One systematic review [106] included four small trials (147 participants with foot ulcers due to diabetes). Data from these studies indicated that hyperbaric oxygen therapy (HBOT) significantly reduced the risk of major amputation and may have improved the rate of healing at 1 year. However, the authors of the review warned that in view of the small size, methodologic shortcomings, and poor reporting of the studies, this finding should be interpreted cautiously. One subsequent small RCT (28 participants) [107] found that ulcer diameter decreased significantly more in the treatment group by 15 days.

In view of the doubt about its effectiveness, and the substantial costs associated with its use, the introduction of HBOT for diabetic foot infections, including osteomyelitis, does not appear justified at present.

Implications for practice

In the diagnosis and management of osteomyelitis in the diabetic foot:

- An ESR above 70 mm/h supports a diagnosis of osteomyelitis.
- Superficial swabs from an ulcer or curettage from its edges and base are poor predictors of osteomyelitis, and of the microbial isolates from bone biopsy.
- Plain radiographs have weak predictive value in the diagnosis of osteomyelitis.
- MRI has moderate predictive value in the diagnosis of osteomyelitis.
- The diagnostic accuracy of ^{99m}Tc bone scanning, indium scanning, and anti-granulocyte scintigraphy is inferior to that of MRI in head-to-head comparison.
- The role of FDG PET in the diagnosis of osteomyelitis remains unclear.
- Empirical antimicrobial therapy pending culture and sensitivity data should be based on the severity of the infection and the expected susceptibility of the likely etiologic agent(s).
- Antimicrobial therapy for osteomyelitis generally should last 4–6 weeks, but a shorter duration is sufficient if the entire infected bone is removed, and probably a longer duration is needed if infected bone remains.
- The effectiveness of adjuvant therapy with G-CSF is unclear.
- The effectiveness of HBOT is unclear.

Implications for research

- More data are needed to establish confident estimates of the predictive value of clinical and laboratory tests and imaging studies used in diagnosis of infection.
- Multicenter studies should be considered comparing nonoperative with operative management of foot osteomyelitis in some situations (e.g., perhaps UT B3 IDSA moderate infections).
- To have clinical relevance, RCTs and systematic reviews of antimicrobial therapy should more

precisely define the inclusion criteria for participants and the indication to use a particular agent.

Conclusion

The evidence base for treating bone and joint infections is improving, but much remains to be done. Greater interdisciplinarity, a focus on research questions about whose importance there is consensus, collaboration between multiple centers, and good study design remain challenges for the research community.

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CHAPTER 4

Infective endocarditis

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Case presentation

A 47-year-old man presents to the emergency room with a 1-week history of fever, malaise, and back pain. The patient's symptoms began insidiously, but have been severe enough to keep him home from work for the past 2 days. The patient was previously healthy, but reports having been told he had a heart murmur caused by mitral valve prolapse. He has no significant family history of medical illness. Further questioning reveals that the patient had a tooth extracted 5 weeks prior to presentation. He does not recall having taken antibiotics prior to the extraction (or at any time during the past 2 months). He denies having ever used intravenous drugs.

Physical examination reveals a temperature of 38.3°C (101.8°F), pulse of 90 per minute, and blood pressure of 120/80 mmHg. Diffuse petechiae are seen on the sublingual oral mucosa, and a grade III/VI holosystolic regurgitant murmur is most audible at the apex. Initial lab results are significant for a hemoglobin of 115 g/L (11.5 mg/dL) and an erythrocyte sedimentation rate of 70 mm/h. Urinalysis shows microscopic hematuria. An ELISA for antibodies to HIV is negative.

You admit the patient with a presumptive diagnosis of infective endocarditis, and arrange for three sets of blood cultures to be obtained, spaced so that 12 hours may pass between drawing the first and last set. You wonder whether this patient should be further examined by transthoracic or transesophageal echocardiography.

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Diagnosis

Epidemiology

There are generally five steps to determining whether a particular patient has infective endocarditis (IE). First, the clinician should consider, prior to obtaining any information from diagnostic studies, the probability that any patient with similar demographic and clinical characteristics would develop the disease (i.e., the prior probability of disease). Because IE is an incident disease, it is best to consider probabilities expressed as incidence, rather than prevalence, so as to gauge a patient's risk of developing IE over time.

Reported incidence rates of IE range from 1.6 to 11.6 cases per 100 000 person-years [1–7]. Much of the variation is attributable to the proportion of people who have prosthetic valves, the proportion who use intravenous drugs, and the population's age distribution (older patients having higher incidences of IE [3,6]; Fig. 4.1).

For this patient, the most applicable estimate to consider – that specific to cases of community-acquired, native-valve IE – is 3.56 to 4.81 cases per 100 000 person-years [5]. Though this chapter focuses on suspected cases of community-acquired, native-valve endocarditis, it is important to note that the risk for IE is higher among patients with prosthetic valves, those who use intravenous drugs [8], and those at risk for nosocomial infections. These differences in the prior probability of IE may influence decisions regarding the appropriate use of diagnostic criteria and tests in these populations.

Clinical presentation

The second step in diagnosing IE involves both a careful physical examination, with special evaluation for the common cardiac, neurologic, vascular, and immunologic manifestations of the disease (many of which

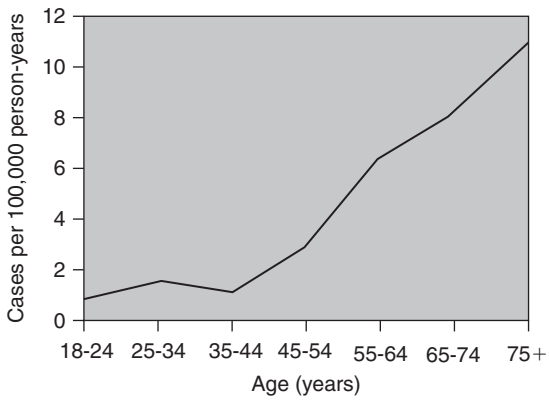

Figure 4.1 Age-specific person-years of community native valve non-IVDU cases residing in six contiguous counties (Philadelphia, Delaware, Montgomery, Bucks, and Chester Counties, PA, and Camden County, NJ) during a 27-month (August, 1988–October, 1990) recruitment period. Person-years of follow-up were calculated by multiplying the population in each age-stratum by 27 months/12 = 2.25 years of case accrual. Data from reference [5]: Berlin JA, Abrutyn E, Strom BL, et al. Incidence of infective endocarditis in the Delaware Valley, 1988–1990. Am J Cardiol 1995;76:933–6.

are listed in Table 4.1), and a medical history focused on whether the patient has any known risk factors for developing IE. With regard to this patient, it is known that patients with mitral valve prolapse (MVP) are 8 to 19 times more likely to develop IE than patients without MVP [9,10]. By contrast, it is useful to know that this patient was HIV-negative, as patients infected with HIV are approximately five times more likely to develop IE (independent of intravenous drug use) [8], with the precise risk being related to the level of immunodeficiency [11]. Other risk factors for IE that have been documented in case–control studies include congenital heart disease [9], prior cardiac valvular surgery [9], rheumatic fever [9], heart murmur without other known cardiac abnormalities [9], previous episodes of IE [9], severe kidney disease [12], diabetes mellitus [12], and prior skin infections [12] or wounds [13].

Blood culture

Third, clinicians should arrange for blood cultures to be obtained prior to the initiation of empiric antimicrobial treatment. Proper timing and technique of blood cultures remain the keys to accurate diagnosis; unfortunately, errors remain common [14]. Multiple blood cultures should be obtained over time so as to demonstrate persistent bacteremia if culturable organisms are present. Valid utilization of the Duke criteria (see below) requires that three independent sets of blood cultures (independent venipunctures) be obtained, with at least 12 hours separating the first and last [15]. More than 99% of cases of true bacteremia or fungemia can be detected with three venipunctures [16,17]. Ideally, each venipuncture should yield at least 15 mL of blood [17], though some culture systems may have different requirements. Organisms commonly associated with community-acquired, native-valve IE are listed in Table 4.2.

Echocardiography

The fourth diagnostic step to be considered is echocardiography. Many studies evaluating patients with confirmed or rejected IE based on pathologic specimens or long-term follow-up have firmly established that transesophageal echocardiography (TEE) has better operating characteristics than transthoracic echocardiography (TTE). For example, in two case series, the sensitivity of TEE for diagnosing IE (in the absence of other clinical information) was 94–100%, and the specificity was 100% [18,19]. By contrast, the sensitivity of TTE in these two series was 44–50%, and the specificity was 93–98%, when the same echocardiographic findings were required for diagnosis [18,19].

TEE is also superior for detecting specific lesions, such as vegetations, perivalvular abscesses, valvular aneurysms, and valvular perforations, that are commonly associated with both the presence of IE and the patient's prognosis [20–29]. In addition, despite early concerns about safety, the procedure carries a very low risk of complication [30].

Despite the superiority of TEE, there are two reasons why it should not be routinely used as a first-line diagnostic test for every patient suspected of having IE. First, among patients with very high or very low probabilities of IE based on history and physical examination, TTE and TEE yield highly concordant diagnostic classifications [31]. Though incorporating the results of TEE improves the sensitivity of the Duke criteria (see below) for diagnosing both culture-positive [32] and culture-negative [33] endocarditis

Table 4.1 The Duke criteria* for diagnosis of infective endocarditis

Major criteria

I Positive blood culture for infective endocarditis

A Typical microorganism for IE from 2 separate blood cultures
- 1 Viridans streptococci (including nutritionally variant strains), *Streptococcus bovis*, HACEK† group, or
- 2 Community-acquired *Staphylococcus aureus* or enterococci, in the absence of a primary focus, or

B Persistently positive blood culture, defined as recovery of a microorganism consistent with IE from:
- 1 Blood cultures drawn more than 12 hours apart, or
- 2 All of 3 or a majority of 4 or more separate blood cultures, with first and last drawn at least 1 hour apart

II Evidence of endocardial involvement

A Positive echocardiogram for IE
- 1 Oscillating intracardiac mass, on valve or supporting structures, or in the path of regurgitant jets, or on implanted material, in the absence of an alternative anatomic explanation, or
- 2 Abscess, or
- 3 New partial dehiscence of prosthetic valve, or

B New valvular regurgitation (increase or change in preexisting murmur not sufficient)

Minor criteria

I Predisposition: predisposing heart condition or intravenous drug use

II Fever: ⩾38.0°C (100.4°F)

III Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions

IV Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor

V Microbiologic evidence: positive blood culture but not meeting major criterion as noted previously,‡ or serologic evidence of active infection with organism consistent with IE

VI Echocardiogram: consistent with IE but not meeting major criterion as note previously

*Adapted from reference [15]. The diagnosis of "definite endocarditis" is made on pathologic grounds when appropriate pathologic specimens from surgery or autopsy reveal positive histology and/or culture. The diagnosis of "definite endocarditis" is made on clinical grounds when 2 major criteria, 1 major and 3 minor criteria, or 5 minor criteria are met. The diagnosis of "possible endocarditis" is given when patients present with findings consistent with IE, but falling short of the requirements for definite endocarditis. The diagnosis of endocarditis is "rejected" if there is a firm alternative diagnosis to explain the clinical manifestations, if there is resolution of the manifestations suggesting IE with ⩽4 days of antibiotic therapy, or if no pathologic evidence of IE is found at surgery or autopsy, in patients who received ⩽4 days of antibiotic therapy.
†*Haemophilus* spp., *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella* spp., and *Kingella kingae*.
‡Excluding single positive cultures for coagulase-negative staphyloccoci and organisms that do not cause IE.

compared to classifications based on TTE results, this improvement is largely confined to (1) patients with intermediate probabilities of IE on clinical grounds, and (2) patients with prosthetic valves [31,32].

The second reason to limit the use of TEE is that it is only cost-effective as a first-line test in these same two groups of patients [34]. Indeed, a detailed decision analysis suggests that among patients with very low (e.g., <2%) probabilities of IE, short-term treatment of bacteremia in the absence of echocardiography is warranted, whereas among patients with high probabilities of disease (e.g., >60%, as might be observed among patients with persistently positive bacteremia without another known cause) it is most cost-effective to treat empirically for endocarditis, regardless of echocardiographic results [34]. This analysis recommends the use of TEE as a first-line test for patients with intermediate probabilities of disease, though initial use of TTE, followed by TEE in the event of negative or inconclusive results, remains a recommended strategy [35].

Regardless of the probability of IE, echocardiography retains an important role in the identification of patients who have complications of IE, such as perivalvular abscess, aneurysm, and valvular perforation. Because TEE is clearly superior to TTE in identifying such complications, it ought to be used whenever complications are suspected, or whenever there is a need to rule them out [21,27]. TEE is also indicated for defining underlying structural abnormalities in that predispose patients to future IE [35].

Table 4.2 Common etiologic agents of community-acquired, native-valve endocarditis*

Organism	Proportion of cases (%)
Streptococcus species	50
Viridans, alpha-hemolytic	35
S. bovis	12
Other streptococci	< 5
Staphylococcus species	30
S. aureus	25
Coagulase-negative	5
Enterococcus species	7
HACEK† group	< 5
Gram-negative bacilli	< 5
Other bacteria/polymicrobial	< 5
Fungi	< 5
Culture-negative	5

*These proportions are approximations based on data from a large number of series. Observed proportions may vary considerably based on features of the local population, including the proportion of intravenous drug users, patients with prosthetic valves, and age distribution.
†*Haemophilus* spp., *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella* spp., and *Kingella kingae*.

Diagnostic criteria

Another reason to use echocardiography is that it enables formal diagnosis of "definite," "possible," or "rejected" IE using the well-established Duke criteria (Table 4.1) [15]. Incorporating clinical, laboratory, and echocardiographic information, the Duke criteria – the fifth diagnostic step in making a diagnosis of endocarditis – have been shown repeatedly [36–40] to have more favorable operating characteristics than the earlier Beth Israel criteria [41]. A retrospective evaluation of 410 patients also showed that the Duke criteria had good agreement (72–90%) with expert clinical judgment [42].

The operating characteristics of the Duke Criteria are best determined using studies, or subgroups within studies, for which the diagnosis of endocarditis was eventually proven or rejected by surgery, autopsy, and/or long-term follow-up. Considering only such studies, and grouping "definite" *and* "possible" categorizations as positive tests, the sensitivity of the Duke criteria is 98–100% [15,36,38–40,43] and the specificity is 93% [44]. If only a "definite" categorization on the Duke criteria is considered as a positive test, the sensitivity drops to 72–80% [15,38,39,43) (69% in elderly patients) [40], while the specificity rises to 99% [44].

The Duke criteria are also valid for diagnosing culture-negative endocarditis, with one study of 49 patients with pathologically proven or rejected IE showing a sensitivity of 72%, and specificity of 100% when serial blood cultures are negative [33]. In light of this reduced sensitivity with retained specificity, several authors have recently proposed modifications to the Duke criteria [43,45,46]. However, we cannot recommend the routine use of any of these proposed modifications until further investigation of their comparative value is available. For example, these studies are uniform in suggesting that the sensitivity of the Duke criteria might be improved, without sacrificing specificity, by adding the serologic diagnosis of Q fever (caused by *Coxiella burnetii*) as a major criterion [45–47]. However, the incremental value of such modifications may only be realized in geographic areas where Q fever accounts for an important proportion of IE cases.

These estimates of sensitivity and specificity are more robust than corresponding estimates of positive and negative predictive values because the latter are strongly influenced by the underlying prevalence of disease in a given population. Nonetheless, predictive values answer the more clinically relevant question of whether a patient with a positive (or negative) categorization using the Duke criteria does (or does not) have IE. One study of the negative predictive value of the Duke criteria suggested it was at least 92% when both "definite" and "possible" categorizations are considered positive tests [48]. Presently, the positive predictive value of the Duke criteria can only be estimated by jointly considering the results of several small, independent samples of patients with pathologically confirmed diagnoses. On the basis of these reports on heterogeneous patient samples, the positive predictive value appears to be ⩾85% for diagnosing both culture-positive and culture-negative IE in patients with native or prosthetic valves [32,33,36].

Proper diagnosis of the presented patient should therefore be based on the Duke criteria, incorporating information obtained from a thorough history and physical examination, three sets of blood cultures, and TEE. If the blood cultures are negative, and the patient is classified as "possible IE" according to the Duke criteria, further diagnostic tests, reviewed elsewhere [33,49–53], may be warranted.

Case presentation (continued)

After overnight incubation, Gram stains of blood culture specimens obtained at 2 of the three separate venipunctures reveal Gram-positive cocci in chains. The following day, these cultures grow viridans *Streptococcus*, and are found to be highly susceptible to penicillin (MIC $\leq$ 0.1 μg/mL) on day 3. Transesophageal echocardiography reveals a moderate-sized, mobile mass attached to the atrial surface of the anterior leaflet of a prolapsed mitral valve, and color Doppler study shows mitral regurgitation with no evidence of extension of the intracardiac lesion. The patient appears hemodynamically stable, and has no evidence of renal dysfunction. Evaluation for signs of congestive heart failure reveals only 1+ edema in the lower extremities. No rales are appreciated, no S3 is audible, and the jugular veins are not distended. A chest radiograph is clear. While deciding upon the most appropriate course of antibiotics, you wonder whether evaluation for mitral valve replacement is warranted.

Antimicrobial management

This patient meets two major criteria in the Duke classification – isolation of a typical organism for IE, and echocardiographic detection of an oscillating mass attached to a valvular leaflet – and is thus classified as having "definite endocarditis." Determination of the most appropriate antibiotic regimen requires consideration of the appropriate agent(s), their dose, route of administration, duration of treatment, and whether such treatment requires prolonged hospitalization.

A working group of the American Heart Association has provided thorough treatment recommendations for IE caused by both typical [54] and atypical [49] organisms. Few randomized trials of these regimens have been conducted because the disease itself is rare, and specific etiologies are rarer still. Recruiting sufficient numbers of patients with IE caused by specific bacteria is therefore difficult. Furthermore, the excellent efficacy of known regimens that would be used in control subjects makes type II errors likely in all but extremely large trials. We will limit our discussion to reviewing the best available evidence on regimens for treating the most common causes of native-valve IE in non-drug users, viridans streptococci and *Streptococcus bovis*.

With few trials to guide treatment recommendations, decisions must be guided by case series documenting the efficacy of various regimens against streptococcal species. The viridans streptococci include several species, such as *S. mutans*, *S. sanguis*, *S oralis* (*mitis*), and *S. salivarius*. The treatment of penicillin-susceptible *S. bovis*, a nonenterococcal, group D streptococcus, is similar, and is often grouped with viridans species in these series.

Four weeks of antimicrobial treatment is traditionally recommended for IE caused by penicillin-sensitive streptococci [54]. Typical regimens include parenteral penicillin, either alone or in tandem with an aminoglycoside. More recently, a single daily dose of intravenous or intramuscular ceftriaxone (2 g/day) for 4 weeks has been shown to be effective in treating endocarditis caused by sensitive strains of streptococci [55–57]. One small randomized trial showed that both this 4-week regimen, as well as a modified regimen of 2 weeks of parenteral ceftriaxone followed by 2 weeks of oral amoxicillin, were curative in all 15 patients receiving each regimen (one possible relapse was noted among the group receiving 4 weeks of ceftriaxone [55]. However, this trial was not adequately powered to determine whether clinically important differences exist in the efficacy of these regimens.

The efficacy of shorter-course (2-week) antimicrobial therapy (typically for patients without longstanding symptoms) has been suggested by uncontrolled studies for 50 years [58,59]. Penicillin alone was initially used in sensitive isolates [58], although more recent series have shown lower relapse rates when an aminoglycoside was added [59,60]. This is attributable to synergistic bactericidal activity between the agents.

Single daily doses of ceftriaxone (2 g/day IV) plus netilmicin (4 mg/kg/day IV) for 2 weeks have recently been shown to be effective, achieving clinical cure in 89% of patients, and microbiologic cure in 100% of patients with documented streptococcal endocarditis [61]. In a randomized trial of 51 evaluable patients, Sexton et al. showed that a 2-week regimen of single daily doses of ceftriaxone (2 g/day IV) plus gentamicin (3 mg/kg/day IV) produced the same 96% cure rate as a 4-week regimen of ceftriaxone alone [57].

Despite these promising results with 2-week therapy, and the tremendous benefits they afford in reducing length of stay in the hospital, several important

considerations may limit their widespread use. First, more extensive evaluation of the efficacy of single daily doses of aminoglycosides is needed. Second, clinicians may be reluctant to add an aminoglycoside for patients at high risk for nephrotoxicity or ototoxicity. Lastly, although isolates of penicillin-tolerant viridans streptococci and *S. bovis* remain uncommon, they have been noted in several recent series [62]. Four weeks of treatment is a prudent option in such cases [62]. A Cochrane Library meta-analysis evaluating the addition of aminoglycosides to standard therapy for endocarditis found greater nephrotoxicity without evidence of definite clinical benefit [63].

Case series suggest that for selected patients with susceptible isolates of viridans streptococci, no evidence of hemodynamic instability, and no other complications of IE, several of these regimens can be safely administered on an outpatient basis [55,56]. However, there have been no published trials directly comparing inpatient and outpatient antimicrobial therapy for IE. Such trials seem unlikely because they would need to be extremely large to detect small, but clinically important differences in the rates of treatment failure. In the absence of such comparative evidence, physicians must weigh, for each individual patient, the risks and costs of remaining in the hospital versus the risks for having IE complications unattended to in the outpatient setting [63].

In summary, there are several viable options for treating patients with penicillin-susceptible, viridans streptococcus or *S. bovis* IE on native valves. These are listed in Table 4.3. If the isolates show relative penicillin resistance (0.1 μg/mL < MIC <0.5 μg/mL), 4 weeks of penicillin (18 million units per 24 hours IV) should be combined with gentamicin (1 mg/kg IM or IV every 8 hours) for at least the first 2 weeks [54,65]. For patients allergic to β-lactam antibiotics, vancomycin hydrochloride (30 mg/kg per 24 hours IV in two equally divided doses) should be used for 4 weeks [54].

Case presentation (continued)

You start the patient on IV penicillin (18 million units per 24 hours), plus IV gentamicin 1 mg/kg every 8 hours. You planned treatment for 2 weeks, but after 2 days, the patient becomes progressively dyspneic at rest. Pulse oximetry reveals an oxygen saturation of 89% on room air. Jugular venous distension is evident at 8 cm above the sternal notch, and rales are auscultated bilaterally. A second chest radiograph reveals patchy infiltrates in the lower lung fields bilaterally.

Surgical intervention

Indications for cardiac surgery

Traditional indications for cardiac surgery in IE include: moderate to severe heart failure, severe valvular dysfunction, perivalvular abscesses, multiple embolic events, prosthetic valve endocarditis, fungal infection, persistent bacteremia despite theoretically adequate antibiotic treatment, and, possibly, the

Table 4.3 Suggested therapeutic regimens for the treatment of native-valve endocarditis due to penicillin-susceptible (MIC < 0.1 mg/mL) viridans streptococci and *S. bovis*

Antibiotic regimen	Dosage and route	Duration
Aqueous crystalline penicillin G sodium	12–18 million units per 24 h IV, continuously or in 6 equally divided doses	4 weeks
Ceftriaxone sodium	2 g once daily IV or IM	4 weeks
Aqueous crystalline penicillin G sodium	12–18 million units per 24 h IV, continuously or in 6 equally divided doses	2 weeks
with gentamicin sulfate	1 mg/kg IM or IV every 8 hours	
Ceftriaxone sodium	2 g once daily IV or IM	
with netilmicin	4 mg/kg daily IV	2 weeks

Modified from reference [5].

echocardiographic detection of large, mobile vegetations [66]. Although 35 years of clinical experience supports the adherence to these indications, the lack of controlled studies makes it difficult to determine the validity or relative strengths of each. In deciding whether to proceed to surgery for an individual patient, careful (and perhaps separate) evaluation of hemodynamic and infectious disease considerations is warranted.

Timing of surgical intervention

Whether proceeding to surgery early (i.e., during the active stage of IE) [67] confers an additional risk for recurrence or mortality remains controversial. There are no randomized trials of the timing of surgical intervention, although one such trial of early surgical intervention compared with medical therapy is ongoing [68]. Clinicians should therefore be mindful that the results of the available cohort studies may be biased if patients with more severe disease, and hence poorer prognosis, were preferentially selected for earlier surgical intervention.

Aranki and colleagues reported that among patients with mitral valve IE, proceeding to surgery before sterilizing the diseased valve with antimicrobial therapy was not associated with a poorer postoperative prognosis [69]. By contrast, among patients with aortic valve IE, delaying operation until the initial IE had healed was associated with more favorable outcomes [70]. Other series show no association between surgery in active IE and poorer prognosis, regardless of the valve involved [71,72].

Several retrospective cohort studies indicate that early surgical intervention may improve short- and/or long-term outcomes in patients with *Staphylococcus aureus* IE [67,73–75] and in any patient with IE complicated by CHF [75,76]. There remains no evidence indicating a benefit to early surgical intervention in patients with uncomplicated streptococcal IE. However, a prospective, randomized trial of medical versus early surgical intervention among patients with uncomplicated IE would be needed to overcome the selection biases that likely influence the foregoing conclusions. Unfortunately, such a trial would still be limited by the inability to blind patients to their received treatment.

Decisions to proceed to surgery must therefore be tailored to the individual patient, and should be based on consideration of at least three groups of factors. First, physicians should consider the patient's risks for operative mortality. Second, physicians should consider the patient's risks for postsurgical complications such as relapse (resumption of the clinical picture of endocarditis, including isolation of the same microorganism, within 6 months of initial treatment), recurrence (development of a new clinical picture also consistent with endocarditis, but with a different microorganism or occurring more than 6 months after the initial episode), embolic events, worsening heart failure, need for subsequent valve replacement, and death. Finally, physicians should consider the short- and long-term prognoses of patients managed surgically versus those managed medically. Several case series have evaluated these prognostic issues.

Prognosis

Relapse and recurrence

Long-term ($\geqslant$10 years) follow-up of inception cohorts of non-intravenous drug users diagnosed with IE suggest that 0–3% of patients will have relapsing IE, and 6–12% will have recurrent IE [29,72,77]. Series of surgically managed patients show a higher (20–25%) incidence of recurrence [78] though, again, the severity of disease may be higher among such patients. Recurrence is more likely in patients with initial IE on a prosthetic valve, those with positive valve cultures at the time of surgery, and in those with persistent fever more than 7 days postoperatively [78]. To monitor for relapses, which typically manifest within 4 weeks of the cessation of treatment, it is recommended that at least one set of blood cultures be obtained in the 8 weeks following completion of antimicrobial treatment [54]. However, the costs and benefits of different strategies have not been evaluated.

The need for subsequent valvular surgery

Several large case series indicate that approximately 10–20% of patients initially operated on for IE will need another valve replacement [77,79,80]. Patients at higher risk for requiring late valve replacement include those with recurrent IE [77], those with initial endocarditis on a prosthetic valve [77], those with initial involvement of the aortic valve [72],) and those with positive cultures of valvular material obtained intraoperatively [80].

Embolic events

Embolic events, typically caused by the fragmentation and dislodging of valvular vegetations, have been reported to occur in 9–44% of patients after being diagnosed with IE [81–83]; many others will have already experienced embolic complications by the time of presentation [83,84]. The variability among these retrospective cohort studies is attributable to differing frequencies of early surgical intervention, heterogeneity in the underlying severity of disease among cohorts, and to whether or not computed tomography was used to detect silent emboli. Once appropriate antimicrobial therapy is initiated, the risk of embolic events decreases precipitously, particularly after the first week of therapy [81,85]. The most common sites for embolization are the central nervous system, spleen, lungs, kidneys, peripheral arteries, retinal artery, and coronary vessels [81–83].

Because of the frequency and substantial morbidity associated with embolic events in IE, and the (untested) premise that early surgical intervention could prevent many embolic events, several investigators have conducted retrospective cohort studies to determine whether patients' risks for embolism could be predicted by echocardiography [81–83,86–89]. The results of these studies have been mixed, depending on the size of study samples, whether TTE or TEE was used, and whether or not computed tomography was used to detect silent emboli. The larger studies using TEE to evaluate vegetations have consistently found that vegetation size (>10 mm) and mobility are each associated with an elevated risk for embolism [83, 87,89]. However, the fact that embolism also occurs in many patients without detectable vegetations raises doubts as to the clinical utility of routinely screening patients for embolism risk using TEE [90].

Congestive heart failure

Symptoms of congestive heart failure (CHF) are found at presentation in more than half of patients with IE. Other patients will experience incident CHF or worsening CHF after the initial infection has healed with appropriate treatment. Patients with native valve endocarditis are more likely to present with CHF symptoms than are those with prosthetic valve endocarditis [28]. Though severe CHF is an indication for early surgery, intractable pulmonary edema and impaired left ventricular systolic function are independent predictors of operative mortality [79].

Early and late mortality

Advances in the diagnosis and management of IE have had substantial impact on overall mortality, though it remains discouragingly high. Recent case series of consecutive patients with IE report survival rates of approximately 75% at 1 year, dropping to approximately 70% at 10 years [29]. Survival is significantly better among patients with initial native valve endocarditis than among those with prosthetic valve endocarditis [29,91].

Among all patients with IE, risk factors for early mortality (typically defined as within 6 weeks of diagnosis) include older age [29] a variety of cardiac complications [29,79,92] and neurologic complications [84,93]. Among patients managed surgically, early postoperative mortality (typically defined as occurring within 30 days of surgery or prior to discharge from the hospital, whichever comes second) occurs in 8–16%, depending on the preoperative clinical severity of the cohort [28,71,79,91]. Risk factors for early operative mortality include older age, *S. aureus* infection, perivalvular abscess with fistulization, worse preoperative heart failure, and preoperative renal failure [28,71,79,94].

Late mortality appears to be greater among men [77], older patients [28,77], patients with *S. aureus* infection [28], perivalvular abscess [27,76,95], and those with initial IE on a prosthetic valve [69].

Case presentation (continued)

Based on this patient's worsening CHF and risk for embolism, mitral valve replacement is performed on the seventh day of admission. Six days later, the patient is stable and discharged to home, where arrangements have been made for him to complete his antibiotic course. Before leaving, the patient inquires as to whether he could have prevented this episode of endocarditis. He also asks what he should do in the future to prevent recurrence.

Antibiotic prophylaxis against infective mendocarditis is no longer recommended for high-risk patients, including those who, like this patient, have MVP and regurgitation, before they undergo many dental,

genitourinary, and gastrointestinal procedures [96]. While this was previously the recommendation, the value of this recommendation has been repeatedly questioned [9,97–99], and there is evidence that many physicians do not follow it [14,100]. In the 2008 update of the American College of Cardiology/American Heart Association guidelines on infective endocarditis, prophylaxis is now recommended *only* for patients at highest risk of poor outcome should they contract endocarditis (prosthetic valves, congenital heart disease, cardiac transplant patients with valve regurgitation) [96].

The low incidence of infective endocarditis makes it unlikely that a randomized, controlled trial of prophylactic efficacy will be undertaken to resolve this question definitively. As a result, several groups have used alternate methods to provide insights into the potential utility of prophylaxis.

Three case–control studies have directly evaluated the efficacy of antibiotic prophylaxis [13,101,102]. The first reported that prophylaxis provides clinically and statistically significant protection against IE [101]. However, this analysis was based on only 8 patients who developed IE and 24 controls, and misclassification of just one of the cases would nullify the results entirely [101]. Furthermore, selective recall of having taken antibiotic prophylaxis among patients with cardiac lesions who did not develop IE may have inflated the observed efficacy. The second and third studies of efficacy, both of which were larger, found no significant benefit of prophylaxis [13,102].

Another approach to quantifying the potential value of prophylaxis is to determine whether procedures known to induce transient bacteremia occur more commonly among patients who develop endocarditis than among those who do not. One hospital-based case–control study [13] and one population-based case–control study [9] have evaluated these risk factors. Both studies found that dental treatments were not associated with an increased risk for IE [9,13], even among patients with known cardiac lesions [9]. Because such patients represent those for whom prophylaxis is recommended [96], the lack of an association between dental treatments and IE in this group suggests that even strict adherence to these recommendations would yield little benefit.

Finally, investigators have conducted formal decision analyses considering both the incidence of IE in patients with mitral valve prolapse who undergo dental procedures, and the incidence of adverse drug reactions following prophylaxis [103,104]. These analyses indicate that prophylaxis is extremely unlikely to produce a net health benefit, and that it could not plausibly provide such a benefit at a cost that society might consider reasonable.

These findings are, perhaps, to be expected considering that only 10.6% of patients who develop IE would have been targets of prophylaxis by virtue of having both a preexisting cardiac lesion and a dental procedure [9]. Therefore, not only does there exist no good evidence supporting the efficacy of known prophylactic regimens, but there is substantial evidence to suggest that prophylaxis could not prevent a sizeable number of IE cases, even if a uniformly effective regimen were developed.

This patient should therefore be told that his episode of IE was an unfortunate occurrence that could not have (reasonably) been prevented with known interventions. Maintaining good oral hygiene with regular flossing may be beneficial [12]. The patient should also be told that his risk for IE is now markedly increased due to both his having had IE in the past, and his having a prosthetic mitral valve [9]. Formal evaluation of the costs and benefits of prophylaxis in such a high-risk population is needed to guide the patient in preventing future episodes.

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CHAPTER 5
Meningitis and encephalitis

Kara B. Mascitti & Ebbing Lautenbach

Meningitis

Case presentation 1

A 30-year-old male presents to the emergency department with a 24-hour history of fever and headache. The patient's symptoms began abruptly and have worsened steadily over the last day. His wife reports that in the last 6 hours he has become somewhat confused. He has no significant past medical or surgical history. He takes no medications and denies alcohol, tobacco, or drug use. His family history is likewise non-contributory. Physical examination reveals a temperature of 38.5°C, a pulse of 110 beats per minute, and a blood pressure of 130/70 mmHg. He does not demonstrate photophobia or neck stiffness. His neurologic examination is non-focal but he is orientated only to person. Initial laboratory evaluation is remarkable for a white blood cell count of 21.4 $\times$ 10^9/L. You admit the patient with the presumptive diagnosis of meningitis, order two sets of blood cultures, and plan to perform a lumbar puncture (LP). You wonder whether to order a computed tomography (CT) scan prior to the LP to rule out an intracranial mass lesion, as well as whether antibiotics can be withheld until after the CT and LP have been performed.

Diagnosis

Epidemiology

The acute meningitis syndrome may be caused by a wide variety of infectious pathogens as well as by noninfectious diseases and syndromes (Box 5.1) [1–5]. Given its frequency and clinical impact, this chapter will focus specifically on acute bacterial meningitis. The annual incidence of bacterial meningitis varies by geographic region, from between

Box 5.1 Differential diagnosis of acute meningitis

Bacteria
- *Streptococcus pneumoniae*
- *Neisseria meningitidis*
- *Listeria monocytogenes*
- *Hemophilus influenzae*
- *Streptococcus agalactiae*
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*
- *Salmonella* spp.
- *Nocardia* spp.
- *Mycobacterium tuberculosis*

Rickettsiae
- *Rickettsia rickettsii*
- *Rickettsia conorii*
- *Rickettsia prowazekii*
- *Rickettsiae typhi*
- *Ehrlichia* and *Anaplasma* spp.

Spirochetes
- *Treponema pallidum*
- *Borrelia burgdorferi*
- *Leptospira* spp.

Protozoa and helminths
- *Naegleria fowleri*

Continued

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Box 5.1 (continued)

- *Angiostrongylus cantonensis*
- *Balisascaris procyonis*
- *Strongyloides stercoralis*
- *Toxoplasma gondii*
- *Plasmodium falciparum*

Viruses
- Nonpolio enteroviruses (Echoviruses, Coxsackieviruses)
- Mumps virus
- Arboviruses
- Herpesviruses
- Lymphocytic choriomeningitis virus
- Human immunodeficiency virus
- Adenovirus
- Parainfluenza viruses type 3
- Influenza virus
- Measles virus

Fungi
- *Cryptococcus neoformans*
- *Coccidioides immitis*
- *Histoplasma capsulatum*
- *Blastomyces dermatitidis*
- *Paracoccidioides brasiliensis*
- *Candida* spp.
- *Aspergillus* spp.
- *Sporothrix schenckii*

Neoplastic diseases
- Lymphomatous meningitis
- Carcinomatous meningitis
- Leukemia

Intracranial tumors and cysts
- Craniopharyngioma
- Dermoid/epidermoid cyst
- Teratoma

Medications
- Antimicrobial agents*
- Non-steroidal anti-inflammatory agents
- OKT3
- Azathioprine
- Cytosine arabinoside
- Immune globulin
- Ranitidine

Systemic illnesses
- Systemic lupus erythematosus
- Vogt–Koyanagi–Harada syndrome
- Sarcoidosis
- Behçet disease
- Rheumatoid arthritis
- Polymyositis
- Wegener granulomatosis
- Familial Mediterranean fever
- Kawasaki syndrome

Miscellaneous
- Seizures
- Migraine
- Serum sickness
- Heavy metal poisoning

Adapted from references [1–5].
*Trimethoprim, sulfamethoxazole, ciprofloxacin, penicillin, cephalosporins, metronidazole, isoniazid, pyrazinamide.

4 and 6 cases per 100 000 adults in developed countries, to up to 10 times higher in less developed nations [6–9].

The incidence of bacterial meningitis has been profoundly affected by the introduction of the *Hemophilus influenzae* type B vaccine in 1987 and the *Streptococcus pneumoniae* conjugate vaccine in 2000. Rates of *H. influenzae* type B disease in children have declined by more than 95% [10], and rates of pneumococcal meningitis in children have declined by almost 70% [11,12]. More recently in 2005, the *Neisseria meningitidis* conjugate vaccine was introduced and, in addition to existing recommendations for use in groups at high-risk of infection, it is now routinely recommended in the US for adolescents before high school entry, which should further reduce the incidence of bacterial meningitis in this age group [13].

The net result of these vaccines and routine immunization programs in developed nations has not only been a reduction in the overall incidence of bacterial meningitis, but also a change in the age distribution of these infections [6]. The median age of persons with bacterial meningitis increased from 15 months in 1986 to 39 years currently [14], such that bacterial meningitis in the US in now predominantly a disease

of adults. Unfortunately, epidemics of bacterial meningitis, especially due to *N. meningitidis*, continue to occur in developing nations, often affecting a large number of adolescents and adults [15]. This chapter thus focuses on bacterial meningitis in the adult population.

Etiology of bacterial meningitis

In an extensive surveillance project of 13 974 cases of bacterial meningitis in the US, 80% of cases were accounted for by *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* [6]. These data were confirmed by several smaller case series of adult bacterial meningitis, which taken together suggest the prevalence of specific organisms to be: *S. pneumoniae* (20–53%), *N. meningitidis* (3–56%), *Listeria monocytogenes* (6–13%), and *H. influenzae* (<8%) [6,8,16–18]. The most likely causative organism depends on several factors including age, immunocompromise, preceding head trauma, recent neurosurgery, and site of acquisition (community-acquired vs. healthcare-acquired) (Table 5.1) [19,20].

While this chapter will focus on community-acquired meningitis, healthcare-acquired meningitis is also a significant problem. The National Nosocomial Infection Surveillance System (NNIS) noted an incidence of 5.6 nonsurgical, healthcare-acquired infections of the central nervous system (CNS) for every 100 000 patients discharged from the hospital between 1986 and 1993, with meningitis accounting for 91% of cases [21]. Unlike community-acquired meningitis, the most common pathogens in healthcare-acquired meningitis are gram-negative bacilli and staphylococci [16,20].

Clinical presentation

Given the documented association between early institution of antimicrobial therapy and both reduced mortality as well as improved neurologic outcomes [22–26], rapid recognition and diagnosis of meningitis is imperative. The relative sensitivity of any given sign or symptom has varied across selected studies published within the past 15 years (Table 5.2) [8,16–18, 27]. Fever is arguably the most common finding, and is often accompanied by other signs or symptoms [19]. Rash, particularly petechiae or purpura, are most common in meningococcal meningitis, but may also be observed in patients with meningitis caused by *S. pneumoniae*, *H. influenzae*, and *L. monocytogenes* [8,16].

The classic clinical presentation of acute meningitis consists of the triad of fever, neck stiffness, and an

Table 5.1 Empiric treatment of bacterial meningitis

Patient population	Likely pathogens	Antimicrobial	Dosage and route	Duration[§]
Immunocompetent	*S. pneumoniae*	Vancomycin[†]	15 mg/kg IV every 6 hours[¶], *plus*	10–14 days
Age 18–50 years	*N. meningitidis*	Cefotaxime Ceftriaxone	2 g IV every 6 hours, or 2 g IV every 12 hours,	
Immunocompetent Age >50 years	*S. pneumoniae* *N. meningitidis* Gram-negative bacilli *L. monocytogenes*	Vancomycin[†] Cefotaxime Ceftriaxone Ampicillin	15 mg/kg IV every 6 hours[¶], *plus* 2 g IV every 6 hours, or 2 g IV every 12 hours, *plus* 2 g IV every 4 hours	14–21 days
Impaired cellular immunity	*L. monocytogenes* Gram-negative bacilli	Ampicillin Ceftazidime	2 g IV every 4 hours, *plus* 50–100 mg/kg IV every 8 hours[‡]	14–21 days
Head trauma, neurosurgery, cerebrospinal shunt	Staphylococci *S. pneumoniae* Gram-negative bacilli	Vancomycin[†] Ceftazidime	15 mg/kg IV every 6 hour[¶], *plus* 50–100 mg/kg IV every 8 hours[‡]	⩾21 days

Modified from references [19,20].

[†] Vancomycin provides additional coverage for penicillin-resistant *S. pneumoniae.*

[¶] Up to a total of 2 g per day.

[‡] Up to a total of 2 g every 8 hours.

[§] Suggested duration of therapy for specific pathogens: *H. influenzae* (7 days), *N. meningitidis* (7 days), *S. pneumoniae* (10–14 days), *L. monocytogenes* (⩾21 days), gram-negative bacilli and staphylococci (21 days).

Table 5.2 Symptoms and signs associated with bacterial meningitis in adults

Author/Year [ref]	N*	Fever (%)	Neck stiffness (%)	Altered MS (%)	Head-ache (%)	Nausea/ vomiting (%)	Focal neuro signs (%)	Rash (%)
Durand 1993 [16]	259	95	88	78	NR	NR	29	11
Sigurdardottir 1997 [18]	127	97	82	66	NR	NR	10	52
Andersen 1997 [27]†	174	99	99	8	NR	52	NR	74
Hussein 2000 [17]	100	97	87	56	66	55	23	10
Van de Beek 2004 [8]	671	77	83	83	87	74	33	26

* Number of patients: 279 cases in 259 patients [16]; 132 cases in 127 patients [18], 103 cases in 100 patients [17]; 696 cases in 671 patients [8].
MS, mental status.
† Limited to cases of *N. meningitidis*.

altered mental status [9]. Recent reviews have found that only 44–67% of patients with bacterial meningitis present with this classic triad [8,16–18]; however, 99–100% of patients will have at least one of these findings [16,18]. It has thus been suggested that the diagnosis of bacterial meningitis may be effectively eliminated in a patient who presents without any of these findings [28].

Cerebrospinal fluid culture

If the diagnosis of bacterial meningitis is a consideration, a lumbar puncture (LP) should be performed promptly [9]. Routine morphologic and chemical analysis of the cerebrospinal fluid (CSF) in suspected bacterial meningitis should include a cell count, white blood cell differential count, glucose concentration, protein concentration, Gram stain, and bacterial culture [4]. The appearance of the CSF in bacterial meningitis is typically turbid and/or discolored with an opening pressure in the range 200–500 mmH_2O (Table 5.3) [4,16–18]. The white blood cell count usually ranges from 1000 to 5000 cells $\times$ 10^6/L (1000 to 5000/mm^3) with greater than 80% neutrophils [4,16–18]. Protein and glucose concentrations are usually 0.1–0.5 g/L (100–500 mg/dL) and $<$2.2 mol/L (40 mg/dL), respectively [4,16–18]. Recent large series of adult meningitis have noted that between 48% and 60% of CSF Gram stains from adults with bacterial meningitis were positive while CSF culture was positive in 65–80% of patients (Table 5.3) [16–18].

Patients partially treated with antibiotics may be less likely to have a positive CSF culture or Gram stain result, but such therapy has minimal effect on CSF indices such as leukocyte count [29]. Even after institution of appropriate antibiotics for meningitis, the CSF picture usually remains abnormal for at least 48–72 hours [30]. On the other hand, CSF pleocytosis, low CSF glucose, and elevated CSF protein may be found even in the absence of infection. Finally, the Gram stain of CSF from patients with gram-negative bacillary or post-neurosurgery meningitis is less often as positive as for pneumococcal and meningococcal meningitis [31].

Blood culture

Blood cultures should also be made in the evaluation of a patient with suspected bacterial meningitis, particularly if a CSF sample cannot be obtained prior to initiation of antibiotics (for example, when neuroimaging is planned prior to LP) [9]. Blood cultures in bacterial meningitis have been noted to be positive in 19–77% of patients [8,18,22,27].

Other diagnostic modalities

Rapid bacterial antigen testing

The use of rapid bacterial antigen testing, or latex agglutination testing, remains controversial. Reviews have noted that only 0.3–3% of all CSF bacterial antigen tests were positive [32–34]. However, the false-positive rate exceeded the true positive rate, and therapy was not altered on the basis of any of the true-positive rapid antigen results [32–34]. The false-positive results led to additional cost, prolonged hospitalization, and some clinical complications. Furthermore, all true-positive CSF samples showed the causative microorganisms by Gram stain [32–34]. In light of these findings, it has been suggested that rapid antigen testing

Table 5.3 Cerebrospinal fluid analysis in bacterial meningitis in adults

Author/ Year [ref]	N*	Opening pressure >300 mm H_2O (%)	Leukocyte count >1000/ mm^3 (%)	Percent neutrophils ⩾80% (%)	Protein >0.2 g/L (%)	Glucose ⩽2.8 mol/L (%)	Gram stain positive (%)	CSF culture positive (%)
Durand 1993 [16]	259	39	28 (>5000/mm^3)	79	56	50 (>2.2 mol/L)	46	83
Sigurdardottir 1997 [18]	127	48	20	88	85 (>0.5 mol/L)	89 (<0.5 mol/L)	57	80
Hussein 2000 [17]	100	NR	56	74	67	72	48	65

* Number of patients: 279 cases in 259 patients [16]; 132 cases in 127 patients [18], 103 cases in 100 patients [17].

should not be used routinely for the determination of the bacterial etiology of meningitis [20]. It may, however, be useful for patients with suspected bacterial meningitis with a negative CSF Gram stain result, or those who have been pretreated with antimicrobial therapy and have negative Gram stain and CSF culture results, although this requires further study [20].

Polymerase chain reaction

Polymerase chain reaction (PCR) of CSF has been used to detect microbial DNA in the CSF of patients with suspected bacterial meningitis. Primers have been developed that permit the simultaneous detection of the most common organisms, including *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* [3]. Several studies have evaluated diagnostic performance of PCR in cases of bacterial meningitis caused by a range of organisms as compared to the gold standard of culture. Reported sensitivities ranged from 94% to 100% and specificity ranged from 91% to 98% [35], suggesting that PCR targeting a broad range of bacterial pathogens might be useful for excluding the diagnosis of bacterial meningitis, although this requires further study [20]. Furthermore, PCR may also have a role in improving diagnosis of bacterial meningitis in patients with negative CSF cultures, but further refinements are needed before PCR can be routinely recommended [20].

Another important role of PCR is in the detection of viral (specifically enteroviral) meningitis. In a multicenter study, 476 CSF specimens were collected from patients with suspected aseptic meningitis [36]: 68 samples were positive for enterovirus by PCR (14.4%), whereas 49 samples were positive by culture (10.4%). The sensitivity and specificity of the enterovirus PCR test (using viral culture as the "gold standard") were 85.7% and 93.9%, respectively. Rapid PCR-based detection of enteroviral meningitis would facilitate early decision-making regarding discontinuation of empiric antibacterial therapy as well as shortened hospitalization.

Neuroimaging

There exists controversy regarding the need to perform neuroimaging prior to the performance of the LP. Despite no evidence, clinicians frequently perform computed tomography (CT) imaging prior to LP in order to rule out intracranial abnormalities which might increase the risk of brain herniation resulting from removal of cerebrospinal fluid during LP [37]. In a survey of 201 physicians who had ordered a CT prior to LP, stated reasons for this practice included suspicion that a focal brain abnormality was present (59%), belief that this practice was standard of care (34%), and a fear of litigation (5%) [38].

The risk of routine CT scanning prior to LP in patients with meningitis is that this practice is associated with a delay in performing LP and initiation of antimicrobial therapy [38]. This delay in initiation of antimicrobial therapy in turn increases the risk of a poor clinical outcome [22–26].

In a study of 235 patients who underwent head CT prior to LP, clinical features associated with an abnormal finding on CT were age >60 years, immunocompromise, history of CNS disease, history of seizure within 1 week before presentation, as well as the following neurologic abnormalities: abnormal

level of consciousness, inability to answer two consecutive questions correctly or to follow two consecutive commands, gaze palsy, abnormal visual fields, facial palsy, arm drift, leg drift, and abnormal language [38]. Of the 96 patients in whom none of these features was present, 93 had a normal CT scan. Although the negative predictive value of the approach was not 100%, the three patients who were misclassified underwent LP without subsequent brain herniation [38]. While these results should be validated in future studies, they suggest that a routine CT scan can safely be avoided in favor of careful evaluation of the clinical findings of patients with suspected meningitis [20,39].

Possible indications for CT or magnetic resonance imaging (MRI) following initiation of therapy include persistent focal neurologic findings, persistently positive CSF cultures despite appropriate antimicrobial therapy, and persistent elevation of CSF polymorphonuclear leukocyte percentage after more than 10 days of therapy [40]. Neuroimaging is also indicated in patients with recurrent meningitis.

Therapy

Case presentation 1 (continued)

The patient undergoes LP without prior CT scanning. CSF reveals an opening pressure of 250 mmH_2O, and the patient is started on vancomycin 15 mg/kg IV every 6 hours and ceftriaxone 2 g IV every 12 hours. Subsequently, the CSF demonstrates a leukocyte count of 2400 $\times$ 10^6/L (2400/mm^3) with 70% neutrophils, protein concentration of 0.32 g/L (320 mg/dL), and a glucose concentration of 3.4 mol/L (62 mg/dL). The Gram stain reveals gram-positive cocci in pairs and chains.

Antimicrobials

Early initiation of antimicrobial therapy is essential in the approach to bacterial meningitis [9]. Early diagnosis and therapy reduce morbidity and mortality, particularly if antimicrobial therapy is initiated before meningitis progresses to a high severity level [8,16,22]. If neuroimaging prior to LP is considered, antibiotics should not be delayed until neuroimaging is complete [9]. In this situation, blood cultures should be obtained and antibiotics then administered [20]. The choice of empiric antibiotic depends on which organisms are most likely causative, which in turn depends on several factors including age, immunocompromise, recent surgery or instrumentation, and local antimicrobial resistance patterns (Table 5.1) [9,20]. Due to the high prevalence of penicillin-resistant *S. pneumoniae*, vancomycin is routinely recommended as part of the initial empiric antibiotic regimen pending culture and susceptibility results [20].

Corticosteroids

Adjunctive corticosteroid therapy for bacterial meningitis remains controversial. Animal studies of meningitis have shown that bacterial lysis resulting from antimicrobial therapy leads to inflammation in the subarachnoid space which in turn may contribute to poor outcomes [41,42]. These studies have also demonstrated that adjunctive corticosteroid therapy reduces cerebrospinal fluid inflammation and subsequent neurologic sequelae [41,42]. A number of randomized controlled trials have examined the possible role of corticosteroid therapy in pediatric meningitis but have come to differing conclusions. A metaanalysis of these trials showed a beneficial effect of adjunctive dexamethasone therapy in reducing severe hearing loss in children with *H. influenzae* type B meningitis and further suggested a similar benefit in reducing hearing loss in those children with pneumococcal meningitis [43].

In adults, early published trials were limited by methodologic flaws and inconclusive results [44–47]. More recently, however, in a multicenter trial of 301 adults with bacterial meningitis randomized to adjuvant dexamethasone vs placebo, administration of dexamethasone (10 mg) at 15 to 20 minutes before or with the first dose of antibiotic (and continued every 6 hours for 4 days) resulted in a statistically significant reduction in the risk of an unfavorable outcome (assessed with the Glasgow Outcome Scale) [48]. Dexamethasone therapy was also associated with a statistically significant reduction in mortality, most pronounced for the subgroup of patients with meningitis due to *S. pneumoniae*. However, there was no significant beneficial effect of dexamethasone therapy on neurologic sequelae, including hearing loss [48]. A recent metaanalysis confirmed these results, showing

that adjuvant corticosteroid therapy reduced mortality from 22% to 12% and reduced neurologic sequelae from 22% to 14% [49].

More recently published studies on the use of dexamethasone as adjuvant therapy for bacterial meningitis in developing countries showed variable results. In areas such as Vietnam where mortality from bacterial meningitis is low, dexamethasone (when given with ceftriaxone) significantly decreased rates of death and disability in cases of proven bacterial infection [50]. However, in Africa, where both HIV prevalence and death rates from bacterial meningitis are high, adjuvant dexamethasone therapy seemed to offer no benefit in terms of mortality or rates of disability [51]. Thus, the debate about the value of corticosteroids in acute bacterial meningitis in developing countries will likely continue [52].

Currently, for patients in the US, routine adjunctive dexamethasone therapy is recommended in the initial treatment of those patients with suspected *S. pneumoniae* meningitis [20,53], but should only be continued if the CSF Gram stain reveals gram-positive diplococci or if blood or CSF cultures are positive to *S. pneumoniae* [20]. The ultimate role of dexamethasone in the treatment of other types of bacterial meningitis, however, needs to be clarified in future studies. In particular, future studies should focus on the possible reduction by corticosteroids of penetration of certain antibiotics (especially vancomycin) into the CNS [54]. Dexamethasone reduces blood–brain barrier permeability and may impede the penetration of vancomycin into the subarachnoid space [54]. This issue is especially relevant as the use of vancomycin for suspected bacterial meningitis increases because of concern regarding the continued emergence of penicillin-resistant *S. pneumoniae* [20]. Of note, while treatment with dexamethasone did not reduce vancomycin levels in the CSF in children with bacterial meningitis [55], treatment failures have been reported in adults who received standard doses of vancomycin and adjunctive dexamethasone [56].

Preventive therapy

Hemophilus influenzae

Currently available *H. influenzae* type B conjugate vaccines are highly immunogenic with more than 95% of infants developing protective antibody concentrations after a primary series of two or three doses. Use of this vaccine has been extremely effective at reducing the incidence of *H. influenzae* meningitis worldwide, often by more than 90% [57,58]. The American Academy of Pediatrics recommends that all infants should receive a primary series of *H. influenzae* vaccine beginning at 2 months of age [59].

Streptococcus. pneumoniae

Use of the 23-valent pneumococcal vaccine to prevent bacteremic pneumococcal disease is recommended in certain high-risk groups [60]. The efficacy of this vaccine against meningitis due to *S. pneumoniae* has never been specifically proven, but has been suggested to be approximately 50% [61,62]. The more recently developed heptavalent pneumococcal conjugate vaccine (PCV-7) has been demonstrated to have excellent efficacy in the prevention of invasive pneumococcal disease in infants and children [63], and its use is now recommended in all infants under 2 years of age [64]. Use of the conjugate vaccine is not, however, currently recommended in adults owing to limited experience in this population. Reductions in invasive pneumococcal disease rates due to the heptavalent vaccine have recently leveled off due to increases (albeit relatively small) in infections caused by non-PCV7 serotypes. Expanded-valency conjugate vaccines for children are currently in clinical trials [65].

Neisseria meningiditis

Routine meningococcal vaccination is currently recommended for certain high-risk groups which include [66]:

- college freshmen living in dormitories
- microbiologists who are routinely exposed to isolates of *N. meningitidis*
- military recruits
- persons who travel to or reside in countries in which *N. meningitidis* is hyperendemic or epidemic, particularly if contact with the local population will be prolonged
- persons who have terminal complement component deficiencies
- persons who have anatomic or functional asplenia.

There are currently two available meningococcal vaccines which both cover serotypes A, C, Y, and

W-135. The polysaccharide vaccine is recommended among eligible children age 2–10 and adults >55 [66]. A more recently approved conjugate vaccine is preferred among eligible people ages 11–55 [66]. The polysaccharide vaccine is not recommended for use in children age <2 due to poor immunogenicity and relatively short duration of protection [66]. The conjugate vaccine has not been studied in this group.

In addition to these high-risk groups, it also recommended that all children age 11–12 be routinely vaccinated with the conjugate vaccine due to the high risk of meningococcal disease among adolescents and college students [66].

In addition to routine vaccination, both vaccine types are also recommended for use in control of meningococcal outbreaks. While sufficient experience exists to recommend vaccination in controlling outbreaks due to serogroup C meningococcal disease only, use of either vaccine may be applicable to control of outbreaks due to other vaccine preventable serogroups (A, Y, and W-135). [66] The conjugate vaccine is preferred over the polysaccharide vaccine if the population targeted for vaccination includes people ages 11–55 [66].

Prognosis

Case presentation 1 (continued)

The patient's CSF culture subsequently demonstrates growth of *S. pneumoniae*, which is resistant to penicillin but susceptible to ceftriaxone. Vancomycin therapy is thus discontinued. The patient's fever, headache, and confusion resolve by day 3 of therapy, although the patient now complains of mild ataxia. He completes 14 days of therapy with ceftriaxone and his ataxia has resolved by the time of his hospital discharge.

While almost uniformly fatal in the pre-antibiotic era, the impact of bacterial meningitis remains great today. Mortality rates in meningitis in recent series have ranged from 19% to 37% [3,8,16–18].

Several factors have been associated with increased mortality in patients with bacterial meningitis including advanced age [8,16,18,22], obtunded mental state [8,16,22], seizures [8,16,22], hypotension [8,22], and platelet count of less than 100×10^6/L (100 000/mm^3) [27]. A recently published prediction model found that six variables routinely available within 1 hour of admission (age, heart rate, Glasgow Coma Scale score, presence of cranial nerve palsies, CSF leukocyte count, presence of gram-positive cocci on CSF Gram stain) reliably predicted unfavorable outcome in adults with bacterial meningitis [67]. Increased fatality has also been associated with absence of typical symptoms and signs, presumably due to a delay in diagnosis [68]. Indeed, despite the recognized association between delay in administration of antibiotics and mortality [22–26], recent evidence notes that the median duration from initial presentation to administration of antibiotics was 4 hours, with 30% of patients waiting longer than 1 hour between performance of an LP and administration of antibiotics [22]. Mortality rates also vary substantially across infecting organisms: *S. pneumoniae* (26–28%); *N. meningitidis* (10–16%), *L. monocytogenes* (32–38%), *H. influenzae* (11–17%), and culture negative (9–10%) [16,18].

CNS sequelae occur in up to 50% of previously healthy patients following meningitis, and include dizziness, tiredness, mild memory deficiencies, gait ataxia, aphasia, seizures, cerebral edema, intracerebral hemorrhage, and hydrocephalus [8,69,70]. In one prospective study, persistent cognitive impairment was detected in 27% of adults despite good recovery from pneumococcal meningitis [71]. Systemic complications of bacterial meningitis may include septic shock, acute respiratory distress syndrome, and disseminated intravascular coagulation [8,70].

Encephalitis

Case presentation 2

A 64-year-old woman is brought to the emergency department by her daughter after a new-onset seizure. The patient had been well until 48 hours prior when she had the abrupt onset of fever and headache. Over the next 2 days, she developed confusion and exhibited bizarre behavior, and subsequently had a seizure. She has no significant past medical history. She takes no medications and does not use alcohol, tobacco, or drugs. The season is spring. The patient is retired and spends most of her time indoors and has not traveled recently. Her daughter recalls no

exposure to animals. On physical examination, she has a temperature of 38.9°C, a pulse of 100 beats per minute, and a blood pressure of 140/64 mmHg. She is minimally responsive, without nuchal rigidity or focal neurologic findings. Her Glasgow Coma Scale score is 8. A serum white blood cell count is normal. A CT scan of the head reveals no intracranial mass lesions. Evaluation of CSF demonstrates a leukocyte count of 500 $\times$ 10^6/L (500 cells/mm^3) with lymphocyte predominance, an elevated protein concentration of 0.98 g/L (980 mg/dL), and a normal glucose. You admit the patient with a diagnosis of acute encephalitis and institute intravenous acyclovir for the possibility of herpes simplex virus-1 encephalitis. You wonder what other diagnostic testing should be done.

Diagnosis

Epidemiology

Encephalitis indicates inflammation of the brain, and is distinguished from meningitis by the presence of abnormal brain function, which may manifest as altered mental status, motor or sensory deficits, or movement disorders [72]. The incidence of acute encephalitis varies according to geographical location but has been estimated at between 5 and 10 cases per 100 000 patient-years (highest in the young and elderly) [72], with approximately 20 000 cases of encephalitis occurring annually in the US [73].

While almost 100 agents have been associated with encephalitis, viruses are by far the most common cause, with the most life-threatening being herpes simplex virus (HSV) and arboviruses [74]. It is important to rule out other potentially treatable conditions that may mimic viral encephalitis (Box 5.2) [75].

Since clinical syndromes and routine laboratory tests are often nonspecific, the diagnosis of viral encephalitis may be difficult. To aid in the diagnosis, certain epidemiologic features should be elicited, including: time of year, location and prevalent disease in the area, recent travel, occupational exposures, recreational activities (e.g., caving or hiking), and animal contacts (e.g., insect or animal bites) [72,73,76]. This chapter will focus primarily on viral encephalitis in adults in the US.

Box 5.2 Diseases that may mimic viral encephalitis

- Abscess or subdural empyema
  - bacterial
  - listerial
  - fungal
  - mycoplasmal
- Tuberculosis
- Cryptococcosis
- Rickettsial infection
- Toxoplasmosis
- Mucormycosis
- Meningococcal meningitis
- Tumor
- Subdural hematoma
- Systemic lupus erythematosus
- Adrenal leukodystrophy
- Toxic encephalopathy
- Reye syndrome
- Vascular disease

Adapted from reference [75].

Etiology of viral encephalitis

Encephalitis resulting from viral infection can manifest as two distinct disease entities:

- Acute viral encephalitis – results from direct invasion of neurons by the virus, with subsequent inflammation and neuronal destruction.
- Postinfectious encephalomyelitis – may occur following a variety of viral infections, usually of the respiratory tract; perivascular inflammation and demyelination of the white matter are prominent.

The most common viruses causing acute encephalitis in the US are enteroviruses, followed by HSV and arboviruses (Box 5.3) [35,77]. Less common viral etiologies include other herpes viruses, adenoviruses, measles, mumps, and the human immunodeficiency virus (HIV). Rare causes of encephalitis such as rabies would be suspected based on exposure and occupational information.

Enteroviral infections (including coxsackieviruses, echoviruses, and polioviruses) peak in the summer and fall, and children and young adults are most commonly affected (Table 5.4) [73].

HSV type 1 is the most common cause of severe nonepidemic viral encephalitis in the US, accounting

Box 5.3 Causative agents for acute viral encephalitis in the United States

Arboviruses
- La Crosse virus
- Eastern equine encephalitis virus
- Western equine encephalitis virus
- St Louis encephalitis virus
- West Nile virus
- Venezuelan equine encephalitis virus
- Powassan virus
- Snowshoe Hare virus
- Jamestown Canyon virus

Enteroviruses
- Coxsackievirus A and B
- Echoviruses
- Poliovirus

Herpesviruses
- Herpes simplex virus type 1
- Herpes simplex virus type 2
- Cytomegalovirus
- Epstein–Barr virus
- Varicella zoster virus
- Human herpesvirus 6
- Simian herpes B virus

Other viruses
- Measles virus
- Mumps virus
- Adenovirus
- Human immunodeficiency virus
- Influenza
- Rabies virus
- JC virus
- Lymphocytic choriomeningitis virus

Adapted from reference [77].

for about 10% of all cases of encephalitis [73,78]. It has a bimodal distribution, with most cases occurring in patients under 20 and over 50 years of age [75,78]. The virus has no seasonal predilection, occurring at any time of the year.

Arthropod-borne viruses (arboviruses) are a heterogeneous group of viruses transmitted by the bite of arthropod vectors (mosquitoes and ticks). They are a common cause of sporadic and epidemic encephalitis

Table 5.4 Seasonal preferences of selected viruses causing encephalitis

Time of year	Virus
Summer/fall	Enteroviruses West Nile virus La Crosse virus Eastern equine encephalitis virus Western equine encephalitis virus St Louis encephalitis
Winter/spring	Measles virus Mumps virus Varicella zoster virus
Any season	Herpes simplex virus type 1 Human immunodeficiency virus Rabies virus

Adapted from reference [73].

in the US and peak in late summer and early fall when exposure to vectors is highest. First documented in the US in 1999, West Nile virus (WNV) is now the most common cause of epidemic viral encephalitis [35,79,80]. The next most common arboviruses causing encephalitis are the California encephalitis (CE) group (La Crosse virus) and the togaviruses: western equine encephalitis (WEE), eastern equine encephalitis (EEE), and St Louis encephalitis (SLE) [35, 81,82]. Venezuelan equine encephalitis (VEE) has also caused small epidemics in Florida, Louisiana, and Texas [83,84] and Powassan virus, which is transmitted by ticks, has caused rare cases in New England [85].

Epidemiologic features may help narrow the diagnosis in arboviral infections, including:
- age of the patient
- location where the infection was acquired
- incidences of other cases of arboviral infections in the area (Table 5.5) [75,86].

Two paramyxoviruses, measles and mumps, are rarely seen now because of effective childhood vaccines, but were significant causes of encephalitis in the pre-vaccine era [73]. In recent years, however, multistate outbreaks of mumps in the US suggest this virus may still be important to consider [87,88]. These infections usually occur in the winter and spring. A postinfectious encephalitis develops in approximately 1 in 1000 cases of measles [89] and

Table 5.5 Epidemiologic features of encephalitis caused by arboviruses in the United States

Virus	Geographical distribution	Age of typical patients	Mortality rate (%)
West Nile	East, mid-west, Gulf coast, southern USA	Adults, esp. elderly	20
La Crosse	Central, eastern USA	<15 years	1
Eastern equine	East, Gulf coast, southern USA	Young children and >50 years	>30
Western equine	West, mid west USA	Infants and >50 years	2–3
St Louis	Central, western, southern USA	>50 years	10–20
Powassan	New England	Any age	50

Adapted from references [75,86].

typically 4–8 days after the rash, during convalescence [81]. Subacute sclerosing panencephalitis (SSPE) is a chronic degenerative disease that presents insidiously with myoclonus and seizure activity an average of 7 years after acute measles infections [86]. CNS disease from mumps, including encephalitis, complicates about 1% of infections [86] and usually occurs in older children or adults. It may occur before, during, or up to 2 weeks after parotid gland swelling or in the absence of parotitis.

Seroconversion to HIV infection and primary HIV disease has been associated with acute, self-limited encephalitis syndromes [81]. Patients with the acquired immunodeficiency syndrome (AIDS) can develop CNS disease from a number of unusual organisms, such as toxoplasmosis, pneumocystis, *Cryptococcus*, cytomegalovirus, and JC polyoma virus (progressive multifocal leukoencephalopathy) [90].

Rabies is transmitted by the bite of an infected animal and is a rare cause of encephalitis in the US. Most human disease in the US is due to bat transmission, although a history of bat bite is uncommon [91]. Other animals that are most often infected include foxes, skunks, and racoons.

Postinfectious encephalomyelitis is an acute inflammatory demyelinating disease that accounts for approximately 10–15% of cases of acute encephalitis in the US [76,92]. It most commonly develops after an infection of the respiratory tract (particularly influenza [93]), a viral exanthema such as measles or varicella, or, in the past, immunization with the vaccinia virus [76,92]. Worldwide, measles is the most common etiologic agent [73]. The pathogenesis is thought to be an autoimmune response triggered by the viral infection, with activation of lymphocytes against myelin [76,92].

Clinical presentation

The triad of fever, headache, and altered level of consciousness is the clinical hallmark of acute viral encephalitis [72,75]. Additional clinical findings often include disorientation, disturbance in behavior and speech, and focal or diffuse neurologic abnormalities such as hemiparesis and seizures [72].

Herpes simplex type 1

The onset of HSV-1 encephalitis (HSE) is usually abrupt, although a subacute prodrome of frontal headache and malaise may occur less commonly. Fever is present in 90% of cases, headache is prominent early in the course of the disease, and the majority of patients have signs suggesting a localized lesion involving one or both temporal lobes [78,94]. These findings often include dramatic personality changes, which may be the first clinical manifestation. Following these behavioral changes, patients may develop aphasia, anosmia, temporal lobe seizures, and hemiparesis. Unlike with HSV-2 meningitis, mucocutaneous herpetic lesions are rarely seen with HSV-1 encephalitis [86].

Arboviruses

The clinical spectrum of illness due to arboviruses is broad, ranging from a mild febrile illness to aseptic meningitis to fatal encephalitis [82,95]. The onset of encephalitis may be abrupt or subacute, and begins with nonspecific symptoms of fever, headache, nausea, and vomiting. CNS symptoms usually begin on day 2 or 3, and symptoms can range widely from only mild deficits to coma [82,96]. Focal abnormalities much as hemiparesis, tremors, seizures, and cranial nerve palsies can occur [82,86,96]. EEE is the most virulent of the arboviral encephalitides and produces symptomatic disease with a high frequency in all age groups and a mortality of 30% [97,98].

In most people, infection with WNV is subclinical or causes a self-limited febrile illness [80,99,100]. Only about 1 in 150 infections results in severe neurologic disease, and advanced age (50 years of age and older) is by far the greatest risk factor for this complication [99]. Encephalitis is more common than meningitis, and symptoms of severe muscle weakness or flaccid paralysis suggestive of Guillain–Barre syndrome may provide a clue to the diagnosis of WNV.

Enteroviruses

While most enteroviral encephalitides are mild, patients with agammaglobulinemia may develop a chronic, lethal form of enteroviral encephalitis [101].

Other herpesviruses

Cytomegalovirus and Epstein–Barr virus can cause acute encephalitis syndromes [78,102,103]. Varicella zoster virus (VZV) infections may also be complicated by encephalitis, which usually develops a week after the exanthema begins [102,104,105]. Acute cerebellar ataxia is the most common complication of chickenpox [73,86,106]. An eruption of herpes zoster may be complicated by encephalomyelitis and granulomatous arteritis, the latter of which has been associated with zoster ophthalmicus [73].

Rabies

The common presentation of rabies is one of agitation, delirium, and hydrophobia, which ultimately progresses to coma and death [107]. The incubation period usually ranges from days to months but may be as long as a year.

Postinfectious encephalomyelitis

The clinical presentation of postinfectious encephalomyelitis resembles that of an acute viral encephalitis, except that there is usually a history of an exanthema or nonspecific respiratory or gastrointestinal illness about 5 days to 3 weeks prior to the onset of CNS disease [86,92].

Laboratory findings

Peripheral white blood cell counts are rarely helpful because they may be normal, slightly elevated, or slightly low [108]. Evaluation of CSF in viral encephalitis reflects the inflammatory nature of the disease, typically demonstrating a mononuclear pleocytosis, ranging from 10 to 2000 $\times$ 10^6/L (10 to 2000 cells/mm^3), an elevated protein level, and a normal or slightly low glucose. Polymorphonuclear cells may be present early in the disease, so it may be useful to repeat the lumbar puncture in 24 hours [109]. CSF PCR to detect viral nucleic acids is the superior diagnostic test in most cases of viral encephalitis; culture of CSF for isolation of viruses has only a sensitivity of 14–24% compared with PCR [35].

In HSE, CSF may be normal in 3–5% of patients [94]. The presence of red blood cells in the absence of a traumatic lumbar puncture is suggestive, but not diagnostic, of necrotizing HSV-1 infection [86]. The availability of CSF PCR techniques to detect HSV DNA has revolutionized the diagnosis of HSE, allowing for rapid, sensitive, and specific diagnosis [35]. In several series, PCR was found to have a sensitivity of greater than 95% with a specificity of 94% to 100%, and it can be positive as early as one day after disease onset [35]. Studies have found no effect on PCR yield during the first week of antiviral therapy, although the sensitivity of the test declines during the second week of treatment [35].

Antibody titers in the CSF or serum are not helpful in establishing an early diagnosis of HSE, and viral cultures are insensitive [35]. HSV antigen is detected later than HSV DNA and has a sensitivity of only 33% [35]. The historical gold standard for diagnosis has been brain biopsy with demonstration of HSV in the brain tissue; however, the sensitivity has been reported to be only 60–70%, possibly because of sampling error or improper specimen handling [35]. For this reason, as well as the less invasive nature of lumbar puncture, PCR has largely replaced the need for brain biopsy [35].

The diagnosis of arboviral infections is usually obtained by serologic assays for virus-specific IgM antibodies on serum and/or CSF. Both acute and convalescent (4 weeks) titers should be measured to confirm acute infection [75]. Viral cultures and PCR testing of CSF, blood, or tissue samples are generally of low yield, except in the case of VEE where blood and throat cultures are frequently positive [86].

A limitation of serologic tests is the possibility of cross-reactivity because of close antigenic relationships among the flaviviruses; for example, patients with WNV may test positive if they had recent infection with SLE or dengue, or vaccination for yellow fever or Japanese encephalitis [99]. A positive IgM test for WNV can be confirmed (eliminate positives caused by cross-reaction) by a WNV plaque-reduction neutralization antibody test (PRNT) titer of greater than 20 [35].

A case of WNV can be confirmed by any one of the following criteria:

- a 4-fold rise in serum antibody titer
- isolation of virus, genomic sequences, or antigen from tissue, blood, CSF, or other body fluid
- specific IgM antibodies in CSF or serum by EIA, confirmed by PRNT [110].

When WNV infection is suspected, CSF should be obtained for PCR or IgM confirmed with PRNT, and PCR should be performed on peripheral blood if CSF is not available [35].

The best diagnostic method for confirmation of rabies is detection of rabies virus RNA in saliva by reverse-transcriptase PCR [75]. Diagnosis may also be made by direct fluorescence antibody staining of viral antigens from a nuchal skin biopsy or brain tissue, isolation of rabies virus in a cell cultures from CSF, saliva, or brain tissue, or a rabies-neutralizing antibody titer of 5 in the CSF or serum in an unvaccinated person [111].

The recommended laboratory tests for viral causes of encephalitis are listed in Table 5.6 [35,77,86].

Other diagnostic modalities

Magnetic resonance imaging (MRI)

MRI with enhancement is superior to CT in detecting early lesions in cases of viral encephalitis, although early in disease both imaging modalities may be unremarkable [112–114]. In HSE, MRI images tend to show lesions in the orbital-frontal and temporal lobes [112,113]. In WNV encephalitis, MR imaging findings can be normal, although abnormal T2-weighted signal can be seen in lobar gray and white matter [114]. MRI is the most helpful test in distinguishing postinfectious encephalomyelitis from viral encephalitis since there is usually pronounced enhancement of multifocal white matter lesions [74].

Electroencephalogram (EEG)

EEG is of value in diagnosing encephalitis, particularly in patients with HSE. Periodic high-voltage spike wave activity and slow-wave complexes emanating

Table 5.6 Recommended laboratory tests in the diagnosis of viral encephalitis

Etiology	Diagnostic tests recommended
Herpes simplex virus type 1	PCR and cell culture of CSF and tissue
West Nile virus	PCR testing of CSF, IgM antibody of CSF and serum (with confirmation by neutralization antibody test)
Other arboviruses†	IgM and IgG antibody of serum and CSF, antigen detection and PCR (brain tissue) available for some viruses
Enterovirus	PCR and cell culture of CSF
Varicella zoster virus	PCR and cell culture of CSF and tissue
Cytomegalovirus	PCR and cell culture of CSF and tissue
Epstein–Barr virus	PCR of CSF and tissue, serum antibody (often inconclusive)
Rabies virus	PCR of saliva or tissue, antigen testing of skin biopsy, brain tissue, or corneal impressions
JC polyoma virus (agent of progressive multifocal leukoencephalopathy)	PCR of CSF, PCR or in situ hybridization of brain tissue
Colorado tick fever virus	Antibody (serum)
Human immunodeficiency virus	Laboratory tests not specific for central nervous system involvement
Herpes B virus	Cell culture or PCR of lesion (special biocontainment laboratory required)
Post-infectious encephalitis‡	Document recent infection at primary site outside CSF

Adapted from references [35,77,86].

PCR, polymerase chain reaction; CSF, cerebrospinal fluid; IgM, immunoglobulin M; IgG, immunoglobulin G.

† Includes common arboviruses in North America including St Louis encephalitis, La Crosse encephalitis, eastern equine encephalitis, and western equine encephalitis.

‡ Post-infectious encephalitis usually caused by measles virus, varicella zoster virus, influenza virus, and vaccinia (pox) virus.

from the temporal lobes at 2- to 3-second intervals are highly suggestive of HSE [75]. However, these findings are not specific for HSE [115].

Therapy

Case presentation 2 (continued)

You order PCR testing of the CSF for HSV. An MRI of the brain reveals enhancing lesions in both temporal lobes. An EEG shows diffuse slowing as well as bilateral periodic discharges in the temporal regions, suggestive of HSE.

Proven antiviral therapy is currently limited to HSV. In two separate trials comparing vidarabine to acyclovir in HSE, acyclovir was found to be superior [116,117]. The recommended dose is 10 mg/kg [4] intravenously every 8 hours for 10–14 days [118]. The dose should be adjusted in patients with renal insufficiency. Both mortality and later sequelae can be substantially reduced if therapy is instituted before there is a major alteration in consciousness [117]. Therefore, early treatment is essential and should be initiated as soon as the diagnosis is suspected. Although several new antiviral drugs with activity against HSV are available in oral formulations with good bioavailability, none has been studied for HSV infections of the CNS. Currently under investigation is the approach of repeat CSF examination after completion of intravenous acyclovir therapy and continuing high-dose oral valacyclovir for 3 months if HSV is still detected by PCR [72].

Treatment of arboviral encephalitis is primarily supportive, as there are no proven therapies. Ribavirin and interferon-2b have been shown to have activity against WNV in vitro, but no controlled trials have been done evaluating these agents [119]. Pooled immunoglobulin from populations previously exposed to WNV offer protection in a mouse model of encephalitis [120] and human studies are currently under way.

Treatment of enteroviral meningitis with pleconaril, an anti-picornaviral agent, has been studied in two clinical trials (one adult, one pediatric) [121]. While no benefit was shown for the primary endpoint of complete resolution of headache, a subgroup analysis showed accelerated headache resolution in patients with moderate to severe disease [121]. No FDA approval for this drug has been pursued at this time.

Treatment of postinfectious encephalomyelitis is largely supportive. The use of corticosteroids is often advocated, but no controlled trails have evaluated their efficacy and safety [92]. There is no established treatment of rabies, short of supportive therapy, once symptoms have begun.

Preventive therapy

There is currently no vaccine available to prevent HSV infection, although several are in preclinical and clinical development [122]. A number of vaccines are also being developed for WNV infection, but none are currently available for human use [79]. A live, attenuated Japanese encephalitis vaccine is available and has been used successfully to reduce the risk of infection in children in China and India [95,123]. Prevention of arboviral infections, however, rests largely on mosquito control and avoidance measures. The live attenuated measles and mumps vaccines are extremely effective in preventing these infections. Recognition of potential exposure to an animal infected with rabies should prompt prophylactic treatment with rabies vaccine and immunoglobulin [124].

Prognosis

Case presentation 2 (continued)

The patient's CSF PCR for HSV is positive and she completes a 14-day course of intravenous acyclovir. She has a slow recovery over several weeks with no clinical evidence of relapse and is transferred to a rehabilitation facility. Six months after the encephalitis, she is living independently but functioning at a lower level than previously and has short-term memory impairment and anosmia.

In the absence of therapy, mortality for HSV-1 encephalitis exceeds 70%, with only 2.5% of patients regaining normal function [75]. Even with acyclovir therapy, morbidity and mortality remain high, with a mortality of 19% and 28% at 6 months and 18 months after therapy, respectively [117]. Poorer outcome was associated with older age, a Glasgow Coma Scale score of <6 at presentation, and the presence

of encephalitis for >4 days prior to initiation of therapy [117].

Many patients who survive are left with severe, debilitating sequelae, including aphasia, anosmia, problems with cognitive function, and motor and sensory deficits [125]. Clinical relapses may also occur after completion of therapy in a small percentage (4–7%) of patients [116,117,126], due to either reactivation of viral infection or proinflammatory immunologic responses [127,128]. Although some authors advocate a longer course of acyclovir therapy (14–21 days) to prevent relapse [126], no definitive evidence exists that a longer duration of therapy is associated with a decreased rate of relapse.

In cases of arbovirus encephalitis, mortality rates and the presence of neurologic sequelae depend on the specific organism and age of the patient, with the extremes of age having worse outcome [75]. The case fatality rate among hospitalized patients with WNV encephalitis is approximately 20%, with advanced age and diabetes identified as risk factors for mortality [99]. Finally, rabies is uniformly fatal in nonimmunized patients [86,107].

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CHAPTER 6

Management of community-acquired pneumonia

David C. Rhew

Case presentation 1

A 63-year-old man presents to your office with fever and a productive cough. His symptoms began 3 days ago. He has hypertension and is being treated with an angiotensin-converting enzyme inhibitor. He does not smoke and has had no recent travel or ill contacts. Does this patient have pneumonia, where antibiotic treatment is warranted, or does the patient have a viral upper respiratory infection, in which case antibiotic treatment may be withheld?

Burden of illness/relevance to clinical practice

Treating patients using an evidence-based approach may ultimately improve care and reduce costs [1–3]. The objective of this chapter is to review the clinical evidence for the management of patients with community-acquired pneumonia (CAP) and to report the highest level of evidence as it pertains to management issues.

MEDLINE, EMBASE, Best Evidence, and Cochrane Systematic Review databases were searched from January 1966 through July 2007 using search terms for the following topics: diagnosis (history and physical examination, chest x-ray, sputum Gram's stain or culture, blood cultures, serology (*M. pneumoniae*, *C. pneumoniae*, *Legionella*, urine legionella antigen), admission decision, empiric antibiotic choice, treatment duration, and prevention (pneumococcal vaccine, influenza vaccine). The American College of Physicians (ACP) Journal Club and the 2007 BMJ *Clinical Evidence* textbook were handsearched to identify additional references. Articles were excluded if they were of non-English language, addressed primarily hospital- or nursing-home acquired pneumonia, focused on pediatrics, or were nonhuman or in vitro studies. Articles in the following order were preferred: metaanalyses of randomized controlled trials (RCTs), systematic reviews of RCTs with no metaanalysis, > RCTs > metaanalyses of non-RCTs, systematic reviews of non-RCTs, nonrandomized or observational studies [4,5].

Case presentation 1 (continued)

Upon physical examination, the patient has a temperature of 38°C (100.4°F), respiratory rate of 32 breaths per minute, pulse of 100 beats per minute, and systolic blood pressure of 145 mmHg and diastolic pressure of 90 mmHg. The examination of the chest is normal. Based on the history, you suspect CAP. However, the chest examination demonstrates no abnormalities. Does a normal chest examination rule out CAP? How confident are you that he has CAP based on the history alone? Should you order a chest radiograph?

Clinical history and physical examination

This type of case is a common scenario for clinicians who practice in ambulatory settings. An important question is the diagnostic accuracy of the history and

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physical examination in making the diagnosis of CAP. A 1997 review [6] identified four prospective studies [7–10] that applied an independent, blind comparison with a reference standard to address this question. The conclusion was that no individual element of the history or physical examination possesses a likelihood ratio high or low enough to rule CAP in or out. This conclusion was also supported by a 2003 systematic review of testing strategies for CAP [11].

The question that follows is whether a *combination* of findings from the history and physical examination can help establish the diagnosis of CAP. Several prospective studies have examined this issue. Diehr et al. [7] assigned points based on the presence of each of the following findings: rhinorrhea (−2 points), sore throat (−1 point), night sweats (+1 point), myalgias (+1 point), sputum production (+1 point), respiratory rate >25 breaths per minute (+2 points), and temperature ⩾37.8°C (100°F) (+2 points). Patients who had a score of −1 or greater were considered to have pneumonia. A threshold score of −1 was associated with a positive likelihood ratio (+LR) of 1.5 and a negative likelihood ratio (−LR) of 0.22. A threshold score of +1 was associated with a +LR of 5.0 and a −LR of 0.47, while a threshold score of +3 had a +LR of 14.0 and a −LR of 0.82.

Singal et al. [9] estimated the probability of CAP based on the following formula: $1/(1+e^{-Y})$, where Y= –3.095 + (1.214, if cough present) + (1.007, if fever present) + (0.823, if crackles present).

Heckerling et al. [10] estimated the probability of pneumonia by first determining how many of the following five findings were present: (1) absence of asthma, (2) temperature >37.8°C (100°F), (3) decreased breath sounds, (4) crackles, and (5) heart rate >100 beats per minute. The number of findings in combination with the prevalence (i.e., pretest probability) of pneumonia could then be applied to a nomogram to determine the post-test probability of pneumonia. The prediction rule had good discriminative ability, with a receiver operating characteristic (ROC) area of 0.82 in the derivation cohort and ROC areas of 0.82 and 0.76 in the two validation cohorts.

In another study, Gennis et al. [8] proposed that chest radiographs be obtained for one or more of the following: respiratory rate >30 breaths per minute, heart rate >100 beats per minute, and temperature ⩾37.8°C (100°F). The presence of any these vital sign abnormalities was associated with a +LR of 1.2. The absence of all of these vital sign abnormalities was associated with a −LR of 0.18 for diagnosing pneumonia.

According to a national survey, 5% of patients with cough have pneumonia [12]. Assuming this pretest probability, and applying the above prediction rules to our patient, the Diehr rule [7] would predict a probability of CAP of 42%, the Singal rule [9] a probability of 29%, the Heckerling rule [10] a probability of 3%, and the Gennis rule a probability of 6%. This wide variability illustrates the difficulty in estimating the "true" probability for CAP by applying prediction rules. Moreover, a prospective observational study by Emerman et al. [13] has found that physician judgment is more sensitive (86%) in predicting CAP than any of the four prediction rules (Diehr, Singal, Heckerling, and Gennis).

Chest radiograph

The gold standard for confirming pneumonia remains the chest radiograph (CXR) [11]. However, do findings from the CXR influence care? A prospective randomized study of patients with acute cough (lasting less than 1 month) found that physicians may miss pneumonia based on clinical findings alone and that the increased use of CXR may result in more frequent appropriate treatment [14]. One observational study of patients with suspected pneumonia showed that CXR findings influence medical management in 69% of cases [15]. Finally, it should be noted that a negative CXR in a patient with presumed pneumonia does not necessarily warrant discontinuation of antibiotics. Some patients hospitalized with presumed pneumonia but who have a negative CXR have been shown to have serious lower respiratory tract infections resulting in bacteremia and death [16]. For these patients, continuation of antibiotic treatment would be justified.

Case presentation 1 (continued)

You decide to order a CXR, and the CXR demonstrates the presence of a left lower lung infiltrate without pleural effusion. Should you admit the patient to the hospital? Do you need to order any other tests to help you make this decision?

Admission decision

The decision to admit the patient to hospital or treat in the ambulatory setting may be facilitated by applying a prediction rule. In this case, the prediction rule provides the clinician with the probability that a specific adverse outcome (e.g., death) is likely to occur, based on the presence or absence of patient-specific factors at the time of presentation. The rationale is that patients deemed to be at low risk for adverse outcomes may be safely treated in the ambulatory setting, while those considered to be at higher risk may require hospitalization. However, there are no randomized controlled trials that directly demonstrate the benefit of such prediction rules.

The modified British Thoracic Society prediction rule [17] has been derived and validated in the largest cohort ($n = 1068$) of CAP patients outside of the US. The modified British Thoracic Society rule assigns 1 point for each of the following findings at the time of initial assessment: (a) **c**onfusion; (b) **u**rea >7 mmol/L; (c) **r**espiratory rate ⩾30/min; (d) low systolic (<90 mmHg) or low diastolic (⩽60 mmHg) **b**lood pressure; and (e) age ⩾**65** years. Patients who receive a score of 0–1 (group 1) have a 30-day mortality rate of 1.5% and are considered appropriate candidates for ambulatory management. Patients who receive a score of 2 (group 2) have a 30-day mortality rate of 9.2% and may be eligible for brief hospitalization or supervised ambulatory care. Patients with a score of 3–5 (group 3) have a 30-day risk of death of 22% and should be treated in the hospital.

The prediction rule that has been most extensively validated is the rule developed by Fine and colleagues [18]. This prediction rule (sometimes referred to as the Pneumonia Severity Index [PSI] or Fine Prediction rule) and the corresponding score (sometimes referred to as the Patient Outcomes Research Team [PORT] score) was retrospectively derived from a cohort of 14 199 patients with CAP from the 1989 MedisGroups comparative hospital database and prospectively validated in a cohort of 38 039 patients with CAP from the 1991 Pennsylvania MedisGroups database. According to the PSI [18], risk factors for worse outcomes are associated with a point score. Age is often the most important risk factor, with one point given for each year of age (with 10 points subtracted for women). Other risk factors receive individual scores that range from 10 to 30 points. These include patient demographics, comorbid conditions, physical examination findings, and laboratory results. Patients who receive a score ⩽70 (class I or II) have an attributable risk of death within 30 days of <1% and are considered appropriate candidates for ambulatory management. Patients who receive a score of 71–90 (class III) have an associated 30-day mortality rate of up to 2.8% and may be eligible for brief hospitalization, or alternatively, ambulatory management with close follow-up [19,20]. However, in one retrospective study [21] ($n = 1889$), one-third of patients who fulfilled low-risk criteria (class I–III) had one or more contraindications to ambulatory care, and for this group of patients, inpatient care was still warranted. This demonstrates that such prediction rules do need to be superseded by clinical judgment. Patients with scores 91–130 (class IV) have a 30-day risk of death of between 8.2% and 9.3%, and patients with score >130 (class V) have a 30-day risk of death between 27.0% and 31.1%. It is recommended that class IV and V patients be treated in the hospital [18].

Case presentation 1 (continued)

The complete blood count and serum chemistries are all within normal limits. You calculate that the patient has a PSI score of 83 (class III) and contemplate admitting him to the hospital. If you admit the patient, what diagnostic tests should you order? What is the value of ordering a sputum Gram stain and culture? What about blood cultures? Should you order tests to detect the presence of 'atypical' pathogens (*Mycoplasma*, *Chlamydia*, *Legionella*)?

Diagnostic tests

Sputum Gram stain and culture

To decide whether or not to order a diagnostic test, it is first necessary to understand the test's diagnostic characteristics (e.g., sensitivity, specificity, positive and negative likelihood ratios, receiver operating characteristic [ROC] curves) [22]. A 1996 metaanalysis evaluated the sensitivity and specificity of sputum Gram stain in community-acquired pneumococcal pneumonia [23]. Inclusion criteria included: confirmed diagnosis of pneumococcal CAP, comparison to an independent reference standard, and all patients being properly

accounted for (i.e., enough data provided to construct a 2 × 2 table of true positives, true negatives, false positives, and false negatives). Three blinded reviewers assessed the quality of the studies to determine eligibility for this review. A total of 12 studies published between 1966 and 1993 met inclusion criteria. These 12 studies enrolled a total of 1322 patients and evaluated 17 test characteristics. The results demonstrated that the sensitivity of sputum Gram stain ranged between 15% to 100%, and the specificity ranged between 11% and 100%. In 10 of the 17 estimations, sputum culture was the reference standard. The authors noted a trend ($P = 0.07$) for increased interpreter training and greater diagnostic accuracy. The conclusion of this study was that no single estimate of sensitivity and specificity could be determined for sputum Gram stain in pneumococcal CAP, and that the results of sputum Gram staining could be misleading, especially if the interpreter was not well trained.

Clinical studies have demonstrated conflicting results as to whether sputum Gram stain and culture provide useful information in the management of patients hospitalized with CAP. In one prospective study [24] ($n = 533$), sputum samples of good quality were obtained from only 39% (210 of 533) of hospitalized patients. In another prospective study [25] ($n = 74$), sputum Gram stain was unable to identify the pathogen affecting any of 74 hospitalized adult patients with nonsevere CAP. This study also showed that sputum cultures identified pathogens in only 4 (5%) patients. A retrospective study [26] ($n = 108$) analyzed the diagnostic effectiveness of sputum cultures and sputum Gram stains among inpatients with bacteremic pneumococcal pneumonia. The authors concluded that sputum Gram stains had some diagnostic value when moderate or abundant gram-positive diplococci were evident but that the overall results of sputum cultures had limited impact on the diagnosis of pneumococcal pneumonia. Another retrospective study [27] ($n = 184$) examined the value of initial microbiologic studies (MBSs) in adults who were admitted for CAP and managed according to the 1993 ATS guidelines [28]. In this study, 14 patients with severe CAP had their antibiotic regimens changed due to a nonresponse to their initial regimen. Three of these patients had their antibiotic regimens changed based on MBSs, while 11 had empiric antibiotic regimen changes. The mortality rate for patients whose antibiotics were changed based on MBSs was no different from that for patients who had antibiotics changed empirically (67% versus 64%, respectively; *P*-value not reported). The authors concluded that initial MBSs were not warranted except in high-risk patients who were more likely to harbor resistant organisms.

Blood cultures

Clinical studies have demonstrated that the incidence of positive blood cultures in adult patients hospitalized with CAP ranges from 0% to 26.8% [25,27,29–53]. One prospective study ($n = 209$) has shown that the yield from blood cultures increases with worsening severity of illness (PSI class I: 5.3%, II: 10.2%, III: 10.3%, IV: 16.1%, V: 26.7%) [48], while another prospective study ($n = 760$) has not shown this to be the case (PSI class I and II: 8%, III: 6.2%, IV: 4.6%, V: 5.2%) [54]. A retrospective study has found that the yield from patients who have received antibiotics prior to blood cultures is significantly lower than that from patients who have not (0% [0/23] vs 16.6% [5/30] patients, respectively; $P < 0.05$) [55]. The incidence of positive blood cultures in the ambulatory setting is considerably lower than that seen in inpatients. According to a study of 1350 ambulatory patients with a variety of infections including CAP the incidence of positive blood cultures is 1.8% [56], while a study of 204 patients with severe CAP (i.e., requiring ICU) has shown a yield from blood cultures of 21.1% [29]. In summary, these data suggest that blood cultures may provide information on the etiology of pneumonia for patients with CAP, especially for those who are hospitalized and sicker (e.g., requiring ICU care).

An important question is whether blood culture results change clinical management and improve outcomes for patients with CAP. A 1996 metaanalysis [57] demonstrated that bacteremia is associated with an increased risk for death (OR 2.8, 95% CI 2.3–3.6), and a large retrospective study ($n = 14\,069$) has found an association between drawing blood cultures prior to antibiotics and lower 30-day mortality rate (adjusted OR 0.92, 95% CI 0.82–1.02; $P = 0.10$) [58]. Also, several studies have specifically addressed whether drawing blood cultures has an impact on clinical management. A large retrospective analysis of a database ($n = 10\,275$) [59] found that positive blood cultures for penicillin-susceptible

S. pneumoniae in hospitalized patients does not have an impact on fluoroquinolone use. One small retrospective study has shown that the results of blood cultures do not lead to a change in the initial empiric antibiotic regimen [55]. Other studies suggest that the results of positive blood cultures may occasionally change the management of patients with CAP [27,29–35,37–53,60] but do not lower mortality [48].

Serologies

Various types of serologic tests exist for atypical pathogens. For *M. pneumoniae* these include enzyme-linked immunosorbent assay (ELISA), complement fixation, and cold agglutinins; for *C.pneumoniae* microimmunofluorescence is used; and for *Legionella* species immunofluorescence assay [61]. However, results from serologic tests to diagnose "atypical" pathogens often return after the patient has been discharged and do not impact the treatment plan [62].

Urine legionella antigen

The urine legionella antigen test identifies *Legionella pneumophila* serogroup I, which is the most common serogroup causing illness. The sensitivity of the test is 70% and specificity is 100%, with a quick turnaround time [63]. Use of the urine legionella antigen test has been demonstrated to expedite the time to diagnosis of legionella by 5 days [64].

Case presentation 1 (continued)

What empiric antibiotics should you order if you decide to treat your patient in the ambulatory setting? What about the inpatient setting? If a patient is admitted and started on intravenous (IV) antibiotics, when would the patient be stable enough to be switched from IV to oral antibiotics and sent home?

Antibiotic treatment

Ambulatory treatment

There are no RCTs that have compared multiple antibiotic regimens to determine which is the most suitable for ambulatory patients with CAP. A 2005 metaanalysis [65] showed that there was no difference in treatment failure between patients with non-severe CAP who received a β-lactam antibiotic alone versus those who received a regimen that included an antibiotic with activity against "atypical" pathogens. Furthermore, one prospective observational study [66] ($n = 864$) showed that ambulatory CAP patients who received antibiotics in accordance with 1993 ATS guidelines [28] experienced no difference in outcomes (mortality, subsequent hospitalization, medical complications, symptom resolution, return to work and usual activities, health-related quality of life, and antimicrobial costs) as compared to those who received other antibiotics. In summary, the evidence indicates that ambulatory patients with CAP may be successfully treated with either a β-lactam antibiotic or an antibiotic with activity against "atypical" pathogens.

Inpatient treatment

While many clinical trials have compared individual empiric antibiotic regimens, fewer studies have compared multiple different empiric regimens. One metaanalysis suggested that empiric antibiotic treatment with either azithromycin or a respiratory fluoroquinolone was superior to comparator agents in the treatment of CAP. One 2002 metaanalysis [67] showed that azithromycin reduced clinical failures by one-third (random effects odds ratio 0.63, 95% CI 0.41–0.95) as compared with other antibiotics in the treatment of CAP. Another 2002 metaanalysis [68] demonstrated that respiratory fluoroquinolones reduced the incidence of therapeutic failures as compared with macrolides, β-lactam antibiotics, and doxycycline for patients with CAP. However, a more recent metaanalysis [69] found no difference in mortality between empiric antibiotic regimens that covered for "atypical" pathogens versus those that did not cover for "atypical" pathogens in hospitalized patients with CAP.

Some of the largest evaluations of the relationship between the initial choice of antibiotics and clinical outcomes have involved use of administrative databases. A retrospective study [70] ($n = 44\,814$) of hospitalized CAP patients showed that dual therapy with a macrolide plus either ceftriaxone, another cephalosporin, penicillin, or quinolone was associated with a lower 30-day mortality rate and shorter

length of stay than monotherapy with the non-macrolide agent. A retrospective study [71] ($n = 10\,069$) of Medicare patients hospitalized in 10 Western US states during 1993, 1995, and 1997 demonstrated an association between lower 30-day mortality and the initial empiric antibiotic regimens including either a macrolide or fluoroquinolone. Another retrospective study [72] ($n = 12\,945$) used a non-pseudomonal third-generation cephalosporin as a referent and demonstrated that three antibiotic regimens were associated with significantly lower 30-day mortality rates compared to the referent: second-generation cephalosporin plus macrolide, third-generation cephalosporin (non-pseudomonal) plus macrolide, respiratory fluoroquinolone alone. Results from these large retrospective analyses suggest that coverage for "atypical" pathogens with either a macrolide or an anti-pneumococcal quinolone is important in the treatment of inpatients with CAP.

In summary, data are conflicting as to which antibiotic or class of antibiotic is most appropriate for the inpatient treatment of CAP patients. Findings from a 2005 metaanalysis [69] of RCTs suggest that coverage for "atypical" pathogens does not reduce mortality. On the other hand, findings from large observational studies suggest that coverage for "atypical" pathogens is associated with lower 30-day mortality rates for patients hospitalized with CAP. It should also be noted that a 2004 metaanalysis [73] of RCTs has shown that patients hospitalized with CAP can be safely and effectively treated with oral antibiotic therapy.

Duration of treatment

RCTs have compared shorter versus longer courses of antibiotic treatment of patients with CAP.

In these studies, duration of shorter course therapy can be as few as 1 to 7 days [74–93], with rates of clinical resolution not significantly different between the shorter and longer courses of therapy. These data indicate that patients with mild to moderate disease (e.g., PSI I–III) can potentially be treated with antibiotic regimens as short as 1–3 days. Often the antibiotic of choice is azithromycin because of its long half-life [78–80,83–85,92,93]. However, one RCT by el Moussaoui [90] shows that 3 days of oral amoxicillin was just as effective as 10 days of oral amoxicillin for patients with CAP with a PSI score $\leqslant 110$ (i.e., class I–III). Patients with more severe disease (e.g., PSI class IV) may potentially be treated with 5–7 days of antibiotics [77,91].

Prevention

Vaccines

Several metaanalyses [94–101] have evaluated the pneumococcal vaccine in adults. Data from the most recent 2007 [96] and 2004 [94] metaanalyses indicate that the polysaccharide pneumococcal vaccine reduces the incidence of invasive pneumococcal disease in adults and the immunocompetent elderly (55 years and older), but does not reduce the incidence of pneumonia or death in adults with or without chronic illness or in the elderly (55 years and older).

Several systematic reviews and metaanalyses have evaluated the efficacy of the influenza vaccine in elderly persons [102–105], healthy adults [106], and healthcare workers [107–109].

Data from the most recent 2006 metaanalysis by Rivetti and colleagues [104] of RCTs and non-RCTs demonstrates that for the elderly when the influenza vaccine is well matched against the circulating strain of virus, the influenza vaccine is 46% (95% CI 30–58%) effective in preventing pneumonia, 45% (95% CI 16–64%) effective in preventing hospital admission, and 42% (95% CI 17–59%) effective in preventing death due to influenza or pneumonia for elderly patients residing in long-term care facilities (note: vaccine effectiveness = 1 – odds ratio). For elderly patients living in the community, the vaccine is 26% (95% CI 12–38%) effective in preventing hospital admission for influenza or pneumonia and 42% (95% CI 24–55%) effective in preventing all-cause death. Data from the most recent 2007 metaanalysis by Demicheli and colleagues [106] of randomized and non-randomized trials shows that for healthy adults the influenza vaccine is 30% effective (95% CI 17–41%) against influenza-like illness. In cases of laboratory-confirmed influenza infection, when the influenza vaccine matched the circulating strain, the influenza vaccine is 80% (95% CI 56–91%) effective. This decreases to 50% (95% CI 27–65%) when the vaccine does not match with the circulating strain.

Data from the most recent 2006 metaanalyses by Thomas and colleagues [108,109] of RCTs and non-RCTs show that vaccination of healthcare workers

who treat elderly (60 years or older) patients residing in a long-term care facility results in lower incidence of influenza-related illness, but only when the patients are also vaccinated; the results are not significant when only the healthcare worker is vaccinated.

In summary, data from recent metaanalyses indicate that the pneumococcal vaccine reduces the incidence of invasive pneumococcal disease in adults (including the elderly), but does not reduce the incidence of pneumococcal pneumonia or death. Recent metaanalyses on the influenza vaccine demonstrate that the influenza vaccine is effective in preventing death due to influenza or pneumonia for elderly patients residing in long-term care facilities, especially when the healthcare worker is also vaccinated. The influenza vaccine is also effective in preventing influenza in healthy adults.

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CHAPTER 7
Tuberculosis

Peter Daley & Marek Smieja

Case presentation 1

A 40-year-old man, who emigrated from India to Canada 2 years previously, presents with irregular fever and cough for several weeks. He is coughing up thick clear coin-like bits of sputum, sometimes streaked with blood. He had hemoptysis on one occasion. His fever is more marked in the evenings and he has cold sweats at night. He also has marked loss of appetite, and has lost some 10 kg of weight in the past 2 months. He smokes cigarettes but denies drinking alcohol. He works in the construction industry, but has been unable to work for a month.

On examination, the patient is thin, almost to the point of emaciation; the ribs stand out prominently, and the trachea is deviated to the right side. There is a hollow beneath the right clavicle. The skin feels hot and dry to the touch although there is no actual fever. There is dullness to percussion over the apex of the lung. Auscultation reveals moist crepitations and bronchial breathing over the same regions.

A chest radiograph reveals a dense opacity in the right apical region with a small cavity in the middle of the opacity. You admit him to hospital into a negative pressure, aerosol isolation room, and order sputum examination for acid-fast bacilli (AFB) and mycobacterial culture. To your surprise, his first sputum examination is negative for AFB. You wonder whether polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* would help to rapidly diagnose this man's suspected pulmonary tuberculosis.

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Epidemiology

Tuberculosis (TB) is an infectious disease caused by the bacterium *Mycobacterium tuberculosis*, and remains a major cause of morbidity and mortality throughout the world. An estimated 1.7 billion people, or nearly one-third of the world's population, have been infected, and every year there are an estimated 8.8 million new cases and 1.6 million deaths [1]. Global TB incidence was stable in 2005, but prevalence continued to rise [1]. TB was the eighth leading cause of death worldwide in 2002, and is projected to drop to twenty-third by 2030 [2]. TB is second only to HIV as a single cause of infectious disease-related mortality. TB was responsible for the loss of 14.3 million disability-adjusted life-years in 2005 [3]. About 95% of the total burden of TB is in resource-poor countries, especially in southeast Asia and sub-Saharan Africa [4].

Targets set by the World Health Organization (WHO) to achieve 70% case detection and 85% treatment success by 2005 were not met. Global case detection in 2006 was 60% (52–69%) and treatment success was 84% [1]. Interventions to meet the targets set by the Global Plan to Stop TB would cost an additional US$1.1 billion in 2007 [1]. In resource-poor nations, and particularly in sub-Saharan Africa, the HIV epidemic, poverty, displacement of populations caused by war or famine, and lack of comprehensive treatment and control programs have contributed to a resurgence of TB, prompting the World Health Organization to declare a Global Health Emergency in 1993. No country with a severe HIV epidemic has been able to successfully control TB.

In India, which alone accounts for 2 million active TB cases and 0.5 millions deaths per year, a large-scale effort to improve laboratory services, drug supplies and standardized regimens, directly-observed therapy,

and improved reporting methods resulted in a major improvement in the proportion of patients completing therapy. It is estimated that the Revised National TB Control Program in India has prevented more than 1 million TB deaths since 1997 [1].

In contrast with high TB burden resource-poor nations, with annual TB incidence rates of between 60 and 641 cases per 100 000 [1], the USA, Canada, and most industrialized countries have witnessed a steady decline in TB incidence through much of the 20th century. However, between 1985 and 1992, an unexpected increased incidence was observed. This has been attributed in part to the HIV epidemic, to an increased number of refugees from endemic countries, and to delayed recognition and control of inner-city outbreaks by underfunded public health departments [5]. With renewed government commitment, incidence has been declining since 1992, to 4.6 per 100 000 in the year 2006, with a 46% decline observed between 1992 and 2006 [6]. In the year 2006, 26 of 50 American states reported an incidence of 3.5 cases per 100 000 or fewer, the interim goal for the new millennium set out in 1989 by the Advisory Council for the Elimination of Tuberculosis strategic plan of the Centers for Disease Control and Prevention (CDC) [7]. These states, representing over one-quarter of the American population, are classified as "low-incidence states" and targeted for TB elimination. The Advisory Council for Elimination of Tuberculosis defined "eradication" as a level of less than 0.1 cases per 100 000 per year [8].

Risk factors for infection and disease

The principal mode of transmission for *M. tuberculosis* is by airborne droplets, and consequently the primary focus is in the lungs. Infection generally does not manifest as disease, and progression to disease depends on a number of contributing factors. The risk factors for developing TB can be divided into factors that increase the probability of exposure to infection and factors that increase the probability of disease among those who become infected.

Given the low incidence of TB in industrialized countries, the major risk factor for exposure is previous habitation in endemic areas. Refugees and immigrants from TB-endemic areas of the world are at high risk of developing TB because of previous exposure, particularly in their first 5–10 years after arrival [9,10]. Initially, their TB incidence is similar to their country of origin, and after 5 years or more approaches that of their adopted country. Other groups at risk of TB exposure are household or institutional contacts of active TB cases, aboriginals, the homeless, injection drug users, and people in long-term care institutions [5,11–14]. Many of the elderly were exposed to TB in their childhood, particularly if born outside of the USA and Canada, as TB was epidemic throughout Europe and most of the world at that time. The elderly with previous infection are at risk for reactivation, particularly if they have an abnormal chest X-ray film and have never received "preventive treatment" [14], now termed treatment of latent TB infection (LTBI) [15].

Among those previously or concurrently exposed to *M. tuberculosis* infection, a number of risk factors have been shown to predispose to developing active disease. The strongest risk factors are concurrent HIV infection, associated with 50–200-fold increases in TB incidence [16,17]. The Centers for Disease Control and Prevention (CDC) recommend HIV testing in all patients diagnosed with TB [16]. Other risk factors include increasing age, malignancy, silicosis, liver or kidney disease, transplantation and other immunosuppression, chronic use of corticosteroids, alcoholism, malnutrition, gastrectomy, jejunoileal bypass, and diabetes mellitus [15,18]. New drugs such as tumor necrosis factor-alpha blockers, used for patients with severe rheumatoid arthritis, have been found to increase reactivation of TB [19]. In Mexico, indoor air pollution from traditional wood stoves was found to be strongly associated with developing TB (adjusted OR of 2·4) [20]. Smoking is a newly recognized but extremely prevalent risk factor for TB infection [21–25]. One metaanalysis of 16 studies published between 1956 and 2002 found increased pulmonary and extrapulmonary TB among smokers and their children [24] and a further metaanalysis of 33 studies showed a significantly increased risk of latent TB infection, a significantly increased risk of clinical TB and positive associations of smoking with TB mortality and passive smoking with TB [26].

Among new tuberculin skin test converters, 5% develop active TB within 2 years, and a further 5% are estimated to develop TB life-long [27]. These

estimates are derived from studies in the 1950s and 1960s, when TB prevalence in the community was markedly higher than at present. Whether exposure to infection still carries the same risk today is unclear. Among patients with untreated HIV, the risk following exposure to *M. tuberculosis* may be as high as 8% per year, or a cumulative 50% or higher risk of developing active TB [17].

Diagnosis

Clinical presentation

The classic clinical features of active pulmonary TB include chronic cough, hemoptysis, expectoration of thick sputum, and constitutional symptoms such as fatigue or night sweats, anorexia, and weight loss. Although many case series exist, there are few population-based studies that describe symptoms of TB. In a population-based study set in Los Angeles County, in which 12% of patients had HIV, the incidence of cough was 48%, fever 29%, weight loss 45%, and hemoptysis 21% [28]. Cough for 2 weeks or more was only present in 52% of patients with pulmonary TB, while fever of over 2 weeks' duration was present in only 29%. The other population-based study was from the Ivory Coast, where 44% of patients had HIV [29]. In this study, cough was present in 80%, fever in 69%, and weight loss in 74%. Other studies have shown variable results. In one case series from Chicago of 110 patients, where 44 patients had pulmonary TB, only one patient with TB did not have either an abnormal chest radiograph, 2 or more weeks of cough, sputum production, or weight loss [30]. Predictive models have been developed to help better predict who requires hospital isolation in patients with suspected TB [31]. However, although these models were more sensitive than the existing respiratory isolation policy (91% and 82% for two retrospective groups vs 71% for isolation policy), the results are limited to smear-positive patients.

Chest radiograph

The diagnosis of pulmonary TB requires compatible changes on chest radiograph, accompanied by culture or other evidence of infection with *M. tuberculosis*. Radiographic changes depend on how recent the infection is, concomitant medical conditions (such as HIV or diabetes), and host reaction (fibrosis, calcification). Pulmonary TB can be primary or post-primary. Primary TB commonly occurs in the lower lung since the droplet is preferentially inhaled into this region, but may involve any lobe. In about 5% of cases, the primary lesion results in clinical pneumonia, which is seen as a lobar or segmental infiltrate with ipsilateral lymphadenopathy. Multiple lobes may also be involved with gross mediastinal lymph node enlargement with or without pleural effusion. Primary TB is increasingly found in adults with acute TB in outbreaks in Canada and other industrialized countries, as many people have had no prior exposure to TB [32]. The areas of consolidation in primary TB may undergo cavitation, referred to as "progressive primary disease." Occasionally, a completely normal X-ray film may be seen in patients with small parenchymal or endobronchial lesions.

The predictive value and reproducibility of a radiograph system for screening of active TB was assessed in one study [33]. Inter-reader agreement using five broad categories was moderate (kappa values of 0·44–0·56). The adjusted odds of active TB, relative to normal or minor findings or granulomas, was 10·2 (95% CI 3.2–33) for fibronodular changes, 46·1 (95% CI 18–117) for parenchymal infiltrates, and 11.6 (95% CI 3·6–37) for pleural effusion.

Diabetic, compared with nondiabetic patients, more commonly had lower lobe disease and were more likely to have cavitation [34]. HIV-positive patients were more likely to have a primary pneumonia, pleural effusions, and multilobe disease. The X-ray film was altered by immune status: among 135 HIV/TB coinfected patients, CD4 T-lymphocyte count of <200 cells/L were more likely than those with counts >200 cells/L to have hilar adenopathy, and less likely to have cavitation [35].

Chest radiograph may be unable to distinguish active from inactive disease, or to exclude concomitant disease such as lung cancer. In such cases, high resolution CT or gallium scanning may be helpful. In a small case series, CT had 93% sensitivity and 100% specificity for detecting active pulmonary TB; gallium scanning had 100% sensitivity and 82% specificity [36].

Immunologic testing

The tuberculin skin test, and gamma-interferon release by lymphocytes stimulated with mycobacterial antigen, can detect infection with *M. tuberculosis*. Both tests

are discussed extensively later in this chapter, under the heading of prevention of TB. For the diagnosis of active TB, the tuberculin skin test is often positive (>5 mm in HIV or close contact to known active case, otherwise >10 mm). However, due to false positives (from previous BCG vaccination or other mycobacteria) and false negatives (anergy from malnutrition, HIV, or other immune compromise), the skin test is only helpful if unequivocally positive (>20 mm). Even in such cases, lung disease may be due to other causes. At least 25% of patients with acute TB will have false-negative skin tests, although these may convert to positive as the patient is recovering.

The interferon gamma release assay (IGRA) has been shown to be more specific than the tuberculin skin test, correlate better with TB exposure, and be less confounded by BCG vaccination and nontuberculous mycobacterial infection [37]. IGRA cannot distinguish active from latent TB. For the diagnosis of latent TB infection, IGRA and tuberculin skin test have similar sensitivity, but IGRA has greater specificity (Elispot 97.7% and Quantiferon 92.5%) [38]. Discordance between skin test and IGRA is unexplained, as are conversions and reversions of results with serial testing.

The role of IGRA for the diagnosis of active TB in high TB burden countries has been assessed [9]. Among HIV-infected adults, sensitivity is 81–90% but specificity is poor due to indeterminate results. IGRA: CD_4 cell ratio may be helpful for diagnosis. Among HIV-negative adults, current IGRA have no role in the diagnosis of active TB. IGRA do not have prognostic or predictive capacity in active TB. The diagnosis of active TB should generally require the isolation of organism.

Microbiologic testing

Confirmatory diagnosis of active TB requires demonstration of the pathogen in appropriately stained smears together with culture of the organism or amplification of specific RNA or DNA. Although TB can affect any part of the body, the lungs are by far the most commonly affected. Hence sputum, and in the case of children, gastric lavage, is the most commonly examined specimen. Early morning specimens are best. The diagnostic yield of the third sputum specimen is only 2–5%, and so two specimens may be adequate, especially when a second clinic visit can be avoided [40]. Bronchoscopy may be indicated if the patient cannot cough up sputum, although most such patients can be identified by inducing sputum production with hypertonic saline [41]. Bronchial washings, brushings, and biopsy specimens may be obtained, and sputum that is collected immediately after bronchoscopy is frequently positive. A variety of other specimens such as urine, cerebrospinal fluid, pleural fluid, pus, or tissue biopsy specimens can be collected in suspected cases of extrapulmonary TB, but the yield of smear is low. Histopathologic examination may reveal granulomatous inflammation. Fresh or frozen tissue can be cultured for mycobacteria. Formalin-fixed tissue, while inappropriate for culture, may still be subjected to AFB stains followed by PCR.

During specimen collection, patients produce an aerosol that may be hazardous to the healthcare worker or others in close proximity to the patient. For this reason, the workers should use protective masks while collecting the specimens. The specimens must be collected in an isolated, well-ventilated area. Sputum induction is particularly prone to generating aerosols that infect staff and other patients.

Smear examination

Mycobacteria are acid-fast bacteria, which can be demonstrated in appropriately prepared specimens by Ziehl–Neelsen (ZN) or related stains. At least 100 fields, which examine only 1% of the entire smear, must be examined under the oil immersion objective before a specimen is declared negative. To find one acid-fast bacillus per field, there must be a minimum of 10^6 bacilli/mL of sputum; hence if there are 5000 bacilli/mL, there is only a 50% chance of finding the bacillus [42]. Thus the sensitivity of the smear examination is low. In surveys, the smear detects only about 50% of all culture-positive cases. Sensitivity is increased using fluorescent stains as compared to conventional Ziehl-Neelsen method, with similar specificity [43]. For laboratories doing high volume work, fluorescent microscopy has the further advantage of allowing more rapid specimen screening, although specialized instruments and skilled laboratory staff are required [42]. Using newer inexpensive, long-lasting light-emitting diode bulbs can allow conversion of conventional light microscopes to fluorescent capacity. Pretreatment of sputum by physical or chemical means is associated with an increase in smear sensitivity as compared to direct smearing [44].

Whereas a positive AFB smear may be diagnostic in an endemic country, fewer than 50% of AFB-positive sputa in industrialized countries may be due to *M. tuberculosis*. The remainder are due to nontuberculous mycobacteria, including *M. kansasii*, *M. avium intercellulare* complex, and *M. xenopii*. Thus, a positive AFB smear requires confirmation by culture, and, where available, by PCR.

Mycobacterial culture

As sputum AFB stain is insensitive, culture for mycobacteria will markedly improve detection of pulmonary TB. Results of culture by the conventional solid egg media take 2–8 weeks, whereas culture using the BACTEC radiometric system or other liquid media gives results in 4–14 days. Only sputum smear examination and PCR are available rapidly enough to influence the management of the acutely sick patient. Culture is estimated to be 80–85% sensitive, and 98–99% specific. Culture has an analytic sensitivity many times greater than sputum examination, and can detect as few as 10–100 bacilli/mL. However, suboptimal specimen collection or overly aggressive laboratory decontamination may result in false-negative cultures. Newer rapid liquid culture techniques such as MODS are more rapid, sensitive, and less costly than conventional culture [45]. After the colonies grow, they are identified by biochemical tests or, more rapidly, by nucleic acid hybridization. Newer identification tests based on detection of TB-specific antigens show improved performance over biochemical tests, and are very inexpensive [46,47].

Drug susceptibility testing is conventionally performed once an organism has been grown, and takes one more week. With current liquid broth methods, detection and drug susceptibility testing results are often available within 3–4 weeks. Newer colorimetric redox indicator methods are rapid and simple and have 89–100% sensitivity and specificity for rifampin and isoniazid results [48]. Molecular approaches to detection of resistance mutations offer single-day results that are comparable to conventional methods [49].

Nucleic acid amplification tests

Nucleic acid amplification tests (NAAT), whether in-house or commercially produced, are increasingly used to rapidly diagnose TB. They can be used for confirmation of smear-positive sputa, or applied directly for detection from sputum, fluids, or tissue. In low-prevalence countries, AFB-positive smears often represent nontuberculous mycobacteria. PCR is able in such cases to rapidly exclude *M. tuberculosis*, with implications for treatment and infection control. PCR would not be cost-effective in high-prevalence areas, since AFB-positive smears in such settings are virtually diagnostic. In either setting, PCR does not currently replace culture since the latter remains more sensitive, and a cultured organism is required to determine drug susceptibilities and for molecular fingerprinting.

Commercial NAAT applied to respiratory specimens has 96% sensitivity and 85% specificity in smear-positive specimens and 66% sensitivity and 98% specificity in smear-negative [50] but these estimates are suspect as studies are heterogeneous [51]. In-house NAAT applied to respiratory specimens show widely variable performance with high heterogeneity between studies, making summary estimates meaningless [52].

Commercial NAAT applied to pleural fluid demonstrates 62% sensitivity and 98% specificity, but in-house NAAT is highly heterogeneous [53]. Similarly commercial NAAT applied to cerebrospinal fluid gave 56% sensitivity and 98% specificity with variable results from in-house assays [54]. NAAT from tissue taken from suspected TB lymphadenitis showed highly variable performance [55].

Generally, studies reporting diagnostic performance of new tests for TB suffer from methodologic deficiencies, with poor blinding, inappropriate reference standard, no description of selection criteria, and use of discrepant analysis [56]. Guidelines on diagnostic testing have been published and future evaluations should comply with these in order to make results interpretable [57,58].

Since PCR detects virtually all AFB-positive specimens, and a proportion of AFB-negatives, it is being investigated for routine initial specimen examination. However, as *M. tuberculosis* may present in only some 1% of specimens submitted to a laboratory in a low-prevalence country the routine use of PCR is not cost-effective. However, if there is high clinical suspicion of TB, PCR is recommended despite AFB-negative smears [59].

Serological tests

Commercial antibody tests from blood demonstrate inadequate and variable performance for the diagnosis of TB, and are not recommended despite their

widespread use in TB-endemic countries [60–62]. In contrast, adenosine deaminase testing of sterile fluids has excellent performance for the diagnosis of extrapulmonary TB, whether used for pleural fluid [63], pericarditis [64] or peritonitis [65].

Phage-based tests

Mycobacteriophage-based assays have been proposed for detection of TB and detection of drug resistance. Few studies have reported direct application to sputum specimens, but several studies show high sensitivity but low specificity for drug resistance detection [66,67]. Further large-scale work on phage assays has been stopped due to inadequate diagnostic performance.

Molecular fingerprinting

In industrialized countries with a low prevalence of TB, reactivation of latent TB disease accounts for the majority of clinical cases of TB. The uniqueness of cultured isolates can be demonstrated by molecular fingerprinting methods such as IS6110 or spoligotyping [68–71]. The finding of clustered isolates strongly suggests recent transmission, and has been shown in several settings to be much more sensitive than conventional public health contact tracing for identifying community outbreaks. Thus, in an outbreak in Baltimore, only 30% of clustered isolates had been detected by contact tracing. National and international databases are being set up to look for temporal and spatial clustering of *M. tuberculosis* isolates, and will be particularly important in low-prevalence countries for identifying otherwise undetected outbreaks. The worldwide occurrence of a multidrug-resistant "Beijing/W" strain was shown using molecular epidemiologic methods to be present not only in Asia, but as far as New York, Cuba, and Estonia [72].

Case presentation 1 (continued)

Your patient's second and third sputum samples are acid-fast positive for small numbers of characteristic bacilli. A nucleic acid amplification test confirms *M. tuberculosis* and you start him on isoniazid (INH), rifampicin (rifampin), pyrazinamide, and ethambutol. He consents to HIV antibody testing and tests negative. Two weeks later his culture confirms *M. tuberculosis*. One week later, his isolate is found to be fully susceptible to all first-line antituberculous drugs, and you discontinue his ethambutol. You plan to treat him with three drugs for a total of 2 months, followed by a further 4 months of isoniazid and rifampicin. You warn him about potential drug side effects, and prescribe vitamin B6 to minimize his chance of neuropathy. You notify the local public health department to arrange contact tracing. You ask the department about the availability of directly observed therapy (DOT), and wonder about the need for DOT in this man.

Treatment

The aim of treatment is to cure patients, prevent relapses, and avert deaths. The treatment of pulmonary TB has been subjected to numerous randomized clinical trials, primarily in developing and high-prevalence countries, although no systematic review of such trials was identified. A number of studies conducted by the British Medical Research Council in Singapore, Hong Kong, India, and East Africa compared various durations and regimens [73], and found that a combination of INH, rifampicin, and pyrazinamide for 2 months, followed by INH and rifampicin for a further 4 months, resulted in high (>96%) cure rates. The CDC recommends these three drugs, together with ethambutol, for initial treatment of TB [74].

For sputum-negative, culture-positive disease, randomized trials have demonstrated that 4 months or longer of therapy yielded very low relapse rates of 1–4% (depending on initial drug susceptibility) [75]. Inclusion of sputum-negative, culture-negative patients with compatible chest radiographs in these trials, however, suggests that these may have fallen more in the category of treatment of "latent TB infection" rather than necessarily representing active TB. Longer regimens result in higher success rates, but at a cost of lower adherence rates. There is not adequate evidence reporting relapse rate or mortality to compare short and long regimens [76].

There is no evidence to suggest that fluoroquinolones should be included in first-line regimens, and ciprofloxacin substitution has shown higher relapse and adverse event rates [77]. Rifabutin was not superior to rifampin in five trials [78].

In addition to examining the duration of therapy, randomized clinical trials have examined the efficacy of twice-weekly INH and rifampin in the continuation phase versus daily therapy. A Cochrane Library systematic review found that there was insufficient evidence to state that intermittent therapy was as effective as daily therapy [79]. Of 399 patients, intermittent therapy cured 99.5% versus 100% in the daily treatment arm. Relapses were 2.5% and 0%, respectively. However, as only a single trial was identified, the authors conclude that larger studies are required to more precisely estimate long-term cure. Intermittent regimens may be particularly attractive as part of supervised programs in which all doses are administered and witnessed by medical personnel (directly observed therapy, "DOT").

The effect of DOT remains unclear. There are cohort and before-and-after data to demonstrate the effectiveness of WHO's DOTS program, which utilizes DOT and short-course (6-month) therapy [6,80]. However, the program also emphasizes a number of other effective aspects of TB treatment including:

- appropriate laboratory facilities and training for microscopic diagnosis
- providing drugs and establishing conveniently located clinics
- appropriate record-keeping and follow-up.

While this program, properly implemented, has clearly worked in areas such as India [6], it remains unclear to what extent the direct supervision of pill-taking was responsible for the improvements.

In a metaanalysis of six randomized controlled trials of DOT or usual care, Volmink and Garner found no effect of DOT [81]. They note, however, that many of the DOT programs examined had poorly motivated staff and were inconvenient for patients to access. In one RCT of DOT in which patients were given a choice of treatment site, adherence was improved. The authors note that DOT is often more expensive than standard therapy, and requires a paternalistic model of medical care at variance with most other therapies. The authors note that an emphasis on incentives and enablers is probably as important as DOT. In many industrialized countries, DOT is used quite selectively for patients with multidrug-resistant (MDR)-TB, or among homeless people, injection drug users, or other groups at high risk of poor adherence.

Even with DOT, high adherence rates are not assured. Clinical trials of health education, monetary incentives, and reminders have found that monetary incentives were very effective at improving adherence to clinic visits among injection drug users on TB treatment [82]. In one randomized trial, a $5 incentive improved compliance two-fold compared with no intervention or education alone [83].

Adjunctive therapies for TB that have been studied include corticosteroids and immunotherapy, with a large RCT demonstrating more rapid symptom control [84]. A metaanalysis of corticosteroid use concluded that, compared with placebo, steroids were associated with more rapid resolution of pulmonary infiltrates, and did not affect sputum conversion [85]. There is insufficient evidence to recommend steroid treatment for TB pericarditis [86] or pleuritis [87], but it is indicated to reduce death and neurologic deficit in TB meningitis among HIV-negative patients [88].

Immunotherapy with *Mycobacterium vaccae* has been studied in seven trials, and summarized in a systematic review [89]. Immunotherapy was ineffective in altering mortality (OR 1.09; 95% CI 0.79–1.49), or in altering the proportion of study subjects with negative sputum smears or cultures. Immunotherapy was associated with increased local side effects including ulceration and scarring. The authors conclude that immunotherapy does not benefit TB patients.

The treatment of TB in the setting of HIV consists of standard therapies. Duration of treatment is not clear. HIV-coinfected patients tend to do equally well clinically and microbiologically, but they have an increased case fatality and TB recurrence rate, due to HIV effects. Timing of initiation of cotherapy is controversial as mortality is high, but immune reconstitution inflammatory syndrome (IRIS) may cause treatment discontinuation. Early ART is favored [90] and guidelines suggest a delay of only 2–8 weeks in those with CD4+ T-lymphocytes of fewer than 200×10^6/L (200 cells/mL) [91].

Three further interventions have demonstrated effectiveness. First, as TB is an AIDS-defining illness, all coinfected patients should be offered appropriate highly active antiretroviral therapy (HAART). This has not been studied specifically in an RCT, but can be extrapolated from cohort studies indicating high death rates in TB/HIV-coinfected patients in the pre-HAART era, and low mortality among AIDS patients taking appropriate antiretroviral medications (see Chapter 11). Second, secondary prevention with INH given to HIV/TB-coinfected patients was

more effective than placebo in preventing recurrent TB [92]. This study was undertaken in Haiti, and its results are probably generalizable to other developing nations with high prevalence of TB. However, secondary prevention is unlikely to be useful in low-prevalence settings, since reinfection rather than relapse was probably responsible for recurrent TB [93]. Third, HIV/TB-coinfected patients have been shown to benefit from trimethoprim/sulfamethoxazole (TMP/SMX). In an RCT, TMP/SMX was more effective than placebo in preventing death and repeat hospitalization among coinfected patients [94]. However, CD4+ T-lymphocyte counts were not available in that study, and are most likely a better method for stratifying risk among HIV/TB-coinfected patients and for assessing the need for prophylaxis of opportunistic infections.

Drug-resistant TB

The World Health Organization reported in 2008 a global population-weighted proportion of drug resistance among new cases of 17.0% (any resistance) and 2.9% (isoniazid and rifampin resistant or "MDR"). Among previously treated cases, 35.0% had any resistance and 15.3% had MDR. MDR-TB is at critical levels in specific regions of the world, including Estonia, Latvia, the Oblasts of Ivanovo and Tomsk in Russia, and the provinces of Henan and Zhejiang in China. MDR-TB has been associated with poorer response to therapy, higher mortality, and higher treatment costs [95–98]. While no randomized clinical trials of therapy are available to guide optimal management strategies, guidelines suggest at least four drugs to which the organism is known or presumed to be susceptible, with at least 18 months duration of treatment [99]. For pulmonary MDR-TB not responding to multiple chemotherapy, surgical resection has been demonstrated to be effective in a number of case series [100,101].

In 2006, the first reports of extensively drug-resistant TB (XDR) emerged, from South Africa [102]. This strain is resistant to isoniazid and rifampin as well as at least one quinolone and one injectable agent [103]. The mortality in the first report was 100%, with a median survival time of 16 days among 44 patients, all of whom had HIV infection. The strain was clonal and probably nosocomially spread. Since then XDR has been reported from every country with the capacity to detect it [104]. Forty-five countries have at least one XDR case, and the proportion of MDR cases that meet the XDR definition range from 0 to 30% [105]. XDR cases have a significantly worse clinical outcome than MDR [106,107].

Case presentation 1 (continued)

You treat your patient for a total of 6 months. At 1 and 2 months, his sputum smears and culture are negative, and he is unable to produce sputum thereafter. You see him monthly to assess symptoms and adherence. At 4 weeks, his transaminase levels rise to 3 times baseline. As he is asymptomatic, you continue his therapy and these normalize by week 8. He completes therapy and is asked to present 1 year later for X-ray film follow-up. Contact tracing reveals no immediate family or fellow workers with symptoms or a positive TB skin test. You reassure him and his wife that the chances of a future recurrence are very low, and quite treatable if recurrence does occur.

Prevention of TB

Case presentation 2

You are asked to see a 25-year-old asymptomatic woman who recently immigrated to Canada from the Philippines. Her screening intracutaneous 5-unit PPD test is positive at 13 mm of induration. She does not recall any previous skin testing. She received BCG vaccine as a young child and has had no known exposure to active TB among family, friends, or occupational contacts. She denies respiratory symptoms, has an unremarkable clinical examination, and has a normal chest radiograph. You diagnose latent TB infection (LTBI) and recommend INH treatment for 9 months. You measure baseline liver enzymes, and counsel her regarding potential side effects. You wonder whether the BCG vaccine is responsible for her TB skin test reactivity. You have read about a new blood test for TB and wonder if this would provide firmer evidence for *M. tuberculosis* exposure. Finally, you wonder whether a 6-month or 9-month regimen of INH is preferred.

BCG vaccination

Prevention of active TB has focused on two strategies: vaccination of children with BCG (bacille

Calmette–Guérin), and tuberculin skin testing followed by treatment of LTBI. Childhood immunization with BCG has been studied in three separate metaanalyses, which pooled both randomized controlled trials and case–control studies [108–110]. BCG was shown to reduce miliary and meningeal TB by 75–86%, and pulmonary TB in children by 50%. However, great variation in efficacy was seen in different trials, and explained in part by distance from the equator [111]. The disadvantages of routine BCG vaccination include false-positive tuberculin skin tests (see below), which compromises contact tracing and initiation of INH treatment of LTBI; cutaneous abscesses; and occasional disseminated BCG.

The tuberculin skin test

The tuberculin skin test consists of injecting 5 units of purified protein derivative "S" (PPD-S) intracutaneously into the volar aspect of the forearm, and measuring the millimeters of induration in the transverse diameter 48–72 hours later. The tuberculin skin test is a well-validated measure of infection with *M. tuberculosis*. It is not, however, an optimal test for the diagnosis of active disease.

The test measures delayed-type hypersensitivity to mycobacterial antigen. Conversion of the skin test may take 3 months after exposure to infection, and a change of 10 mm or more identifies patients who are at high risk for developing active TB (estimated at 5% in the next 2 years, and a further 5% lifelong) [27].

In the immunocompetent individual without acute symptoms of TB, the test approaches 100% sensitivity [11]. Among patients with acute TB, false negatives of 25% have been reported. Such anergy may be specific for *M. tuberculosis*, or there may be a general anergy to multiple antigens. Anergy is more common among HIV-positive and other immunocompromised patients, or among the malnourished. Although individuals anergic to multiple antigens can be identified by testing intracutaneous responses to candida, tetanus, mumps, or other common antigens, these tests have poor reproducibility and are no longer recommended [112].

False-positive tuberculin skin tests may result from previous BCG vaccination or from exposure to other mycobacteria. A metaanalysis has shown that, while BCG vaccination is associated with skin test positivity, the skin test is rarely >15 mm, and the effects rarely persist beyond 15 years [113]. Other endemic mycobacteria may also cause false-positive tuberculin skin tests, and the cut-off for "positivity" in such areas may need to be >12 mm or >15 mm of induration.

Various cut-off values for interpreting tuberculin skin test positivity have been recommended [114,115]. In India and many areas with high TB prevalence, >12 mm is used as a cut-off for positivity. In the USA, the use of three different cut-off points has been recommended. For patients with HIV, recent contact with a patient with active TB, or signs of previous TB on chest radiograph, a skin test of >5 mm identifies infection. For patients with other risk factors for infection, >10 mm is used as a cut-off. These include immigrants from endemic countries and patients with silicosis, liver or kidney disease, gastrectomy or ileal bypass, the homeless, or aboriginals. In patients at low risk of infection or disease, >15 mm is used. However, testing low-risk individuals with tuberculin skin tests are no longer generally recommended [15]. A fourth criterion for positivity is a change in induration by 5 mm between serial tests. For individuals undergoing screening prior to employment, a baseline tuberculin test may stimulate remote immunity due to previous BCG or *M. tuberculosis* infection. Such "boosting" of immunity is identified by the two-step tuberculin test, in which the skin test is repeated 1 week or more after the initial test. Detection of the boosted response prevents ascribing the boosted response to recent exposure, should the person be retested in the future [116].

Tuberculin testing is recommended to aid diagnosis (see previous discussion) and to identify asymptomatic infected individuals who may be candidates for treatment of LTBI. When contacts of an active case are investigated, a skin test of >5 mm indicates recent exposure and >5% risk of active TB. Such patients have been shown to benefit from monotherapy with INH.

Interferon gamma release assays

Given the difficulties in interpreting the tuberculin skin test, and the need for the patient to return for a second visit, other tests for detecting immune responses to *M. tuberculosis* have been developed [117–120]. Interferon gamma release assays detect interferon produced by an in vitro memory immune response to antigens specific to *M. tuberculosis* such as ESAT-6, CFP-10, and TB 7.7. This test has been shown to correlate well with skin testing [121], and is approved

by the Food and Drug Administration (FDA) in the USA. It is recommended to be used in the USA in place of tuberculin skin test in all testing situations [122]. This test is less influenced by BCG vaccination, correlates better with TB exposure, and is more specific than the tuberculin skin test [37].

Treatment of LTBI

Treatment of latent TB infection is the strategy of treating asymptomatic infected patients to prevent future active TB [11]. INH monotherapy for 6–12 months, rifampicin for 4 months, or rifampicin/pyrazinamide for 2 months, have all been studied in randomized clinical trials of LTBI. The comparator in these trials was either placebo, or INH.

Three metaanalyses for treatment of LTBI were identified. For non-HIV patients, Cochrane reviewers identified 11 randomized trials of INH versus placebo, which enrolled 73 375 people between 1952 and 1994 [123]. They calculated an overall efficacy for INH versus placebo to be a relative risk of 0.40 (95% CI 0·31–0.52, a relative risk reduction of 60%). INH also reduced extrapulmonary TB and TB deaths, whereas all-cause mortality was unchanged (RR 1.10; 95% CI 0.94, 1.28). Durations of less than 6 months were no more effective than placebo. Both 6- and 12-month regimens were more effective than placebo, with relative risks of 0.44 (95% CI 0.27–0.73) and 0.38 (95% CI 0.28–0.50), respectively. Direct comparison of the efficacies of these two regimens is misleading, however, as heterogeneous study populations were randomized in the various studies. In the only direct randomized comparison of 6 versus 12 months [124], relative efficacy was a 65% and 75% reduction, respectively (RR 1.4; 95% CI 0.8–2.4). The difference was not statistically significant. In subgroup analyses, those who took 80% or more of their drug had efficacy of 93% with 12 months' treatment, versus 69% with the 6-month regimen. On the basis of this study, and a reinterpretation of the Alaskan US Public Health Service study [125], the CDC has recommended 9 months of treatment for latent TB infection [11].

In HIV-positive people, two metaanalyses have been published [126,127]. Any prophylaxis regimen was more effective than placebo with a relative risk of active TB of 0.64 (95% CI 0·51–0·81). Those with a positivie tuberculin skin test had more benefit (RR 0.38; 95% CI: 0.25–0.57) than those with a negative tuberculin skin test (RR 0.83; 95% CI: 0.58–1.18). In spite of the reduction in subsequent active TB with preventive therapy, all-cause mortality was not reduced (RR 0·95; 95% CI: 0.85–1.06), although a beneficial estimate.

Other effective regimens studied in randomized trials include rifampicin alone for 4 months, or rifampicin with pyrazinamide for 2 months. The combination of rifampicin with pyrazinamide has been studied in three RCTs, and shown to be at least as effective as INH with similar tolerability [128–130]. Subsequently, a case series reported a number of individuals with hepatotoxicity, including a number of deaths, secondary to the combination of rifampicin with pyrazinamide [131]. The CDC now recommends caution with this regimen [132], and does not recommend this regimen for pregnant women.

Current ATS/CDC recommendations for treatment of LTBI are: 9 (preferred) or 6 months of INH, or 4 months of rifampicin. The 2-month regimen of rifampicin and pyrazinamide should only be considered if the risks justify the benefits. For latent MDR-TB infection, two drugs are recommended to which susceptibility has been demonstrated in the index case. These would usually include pyrazinamide and a quinolone, although one case series demonstrated that this combination is poorly tolerated [133].

In cases exposed to known MDR-TB, the role of prophylaxis is unclear and individual decisions should be made based on risks and benefits [134,135].

Case presentation 2 (continued)

Your patient is treated with daily INH and vitamin B6. She increasingly complains of tiredness and headaches, and difficulty concentrating on her university studies. After 5 months, she has decided that she will not continue with treatment. You convince her to complete 6 months of therapy, which you know to be an acceptable alternative to the full 9 months recommended by the CDC, and she agrees to this. You emphasize to her that treatment for latent TB infection is imperfect and that a small chance of future TB remains. You recommend that, should she ever develop symptoms compatible with TB, she will need to be investigated for this. You estimate that her baseline lifetime risk of TB reactivation was up to 5%, and following treatment, you have reduced this risk to 2% or less.

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CHAPTER 8

Diarrhea

Guy De Bruyn & Alain Bouckenooghe

Case presentation 1

A 52-year-old previously healthy woman is brought to the emergency room with symptoms of vomiting, severe abdominal cramps, and bloody diarrhea. About 3 days prior she developed abdominal pains and diarrhea, that was watery at the time of onset and for which she was given amoxicillin by her family healthcare provider. She got sicker with abdominal cramping and the stools became bloody over the 24 hours preceding admission. Earlier she had twice had spontaneous nose bleeding with loss of only small amounts of blood. No other family members are currently ill, but several co-workers who had eaten lunch with the patient at a local fast-food restaurant developed diarrhea around the same time. She has not traveled outside of her city of residence in the last 6 months.

On physical examination, she appears ill. She complains of severe abdominal pain. Her vital signs indicate she is afebrile, has a mild tachycardia with normal blood pressure. There is remarkable pallor of the conjunctiva. Her abdomen is mildly tender to palpation. Laboratory analysis is as follows: hemoglobin 84 g/L (8.4 mg/dL), hematocrit 24%, platelets 70 $\times$ 10^9/L, lactate dehydrogenase 855 U/L, liver function tests normal, urea 52.8 mmol/L (148 mg/dL), creatinine 548 μmol/L (6.2 mg/dL), reticulocyte count 5.2%, Coombs test negative, coagulation tests normal with exception of mildly elevated fibrin degradation products.

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Diagnosis

Epidemiology

Diarrhea is a syndrome that is readily recognized. Definitions for diarrhea typically use duration as an organizing principle (see glossary at end of chapter), although pathophysiologic or anatomic definitions are also common. In general, the clinical concern is discerning infectious from noninfectious causes, as well as likely pathogens that may be encountered in infectious cases.

Globally, diarrheal diseases are a major cause of mortality and morbidity, accounting for an estimated 1.78 million deaths and 58.7 million disability-adjusted life-years (DALYs) lost [1]. Estimates of incidence of acute infectious diarrhea vary between 0.8 and 100 cases per 100 person-years (Table 8.1). Studies based in general practice settings tend to have lower incidence estimates, reflecting the large number of symptomatic persons who do not seek medical care as well as underascertainment of cases. For every person attending their primary care provider, a further five to six [2] or more symptomatic cases may not seek care [3]. Incidence rates also vary by age, with a bimodal distribution. Infants have the highest rates, with lowest rates in the late teens, rising slightly in early adulthood. Although recent data are scarce, prior reports indicate very high peak age-specific rates of disease in developing countries of 9.7 cases per person year [4]. Healthcare-seeking behavior is modified by age, symptom severity, and duration, and the presence of particular alarm symptoms such as fever or blood in the stool. One study found that in a multivariable logistic regression model, only age, fever, and abdominal cramps were independently associated with seeking medical consultation [3].

Table 8.1 Population-based estimates of diarrheal disease incidence

Location, period	Cohort	Incidence [cases/100 person years] (95% confidence interval)	Reference
Cleveland, 1948–57	Community	150	[158]
Tecumseh, 1965–71	Community	100	
Brazil (urban), 1978–80	Community	143	[159]
Egypt (rural), 1980–1	Community	100	[160]
England, 1993–6	Community	19.4 (18.1–20.8)	[2]
	General practice	3.3 (2.94–3.75)	
Netherlands, 1998–9	Community	28.3 (25.2–31.5)	[3]
	General practice	0.8	

Globally, poor water, sanitation, and hygiene are the greatest risk factors for diarrheal disease [5]. Aside from age, other personal characteristics such as underlying medical conditions (HIV infection, prior gastric surgery, intake of medications that lower gastric acidity) are associated with elevated risk of acquiring diarrhea [6,7], as are other factors including sexual practices [6].

In travelers to tropical or subtropical destinations, diarrhea is amongst the commonest of acute ailments encountered [8]. The attack rate of traveler's diarrhea varies by location, season of travel, consumption of high-risk food or beverages (e.g. tap water, ice cubes, ice cream, food from street vendors, salads, raw or uncooked shellfish), and other factors [8–14]. Rates in expatriates from developed nations may approach that for children under 5 years of age in these locations [12].

Vaccines have been developed against some of these pathogens, with variable degrees of efficacy. The most commonly used traveler's vaccines against specific enteric pathogens include various candidates against *Salmonella typhi* and *Vibrio cholerae.*

Clinical findings

Inquiry regarding certain physical symptoms may assist in defining patients in whom stool cultures are likely to yield pathogenic organisms. Clinicians should enquire regarding duration of symptoms; characteristics of stool (consistency, frequency, volume, and presence of blood or mucus); symptoms of hypovolemia, abdominal cramps, or fever; travel history; recent medications; and ingestion of raw or undercooked meat, unpasteurized dairy products, or raw seafood.

Physical examination should identify hypovolemia. However, the clinical diagnosis of hypovolemia in adults has best been validated in acute blood loss, and remains unproved in volume loss from diarrhea [15]. Therefore, physical findings such as postural vital signs, dry tongue, dry axillae, decreased skin turgor, or prolonged capillary refill time may need to be supplemented by measurement of serum electrolytes, urea, and creatinine to confirm the diagnosis.

The time to clinical presentation varies with causative agent, a point emphasized by data from the GeoSentinel Database. Presentation with acute diarrheal illness due to parasitic infections was more common in returning travelers than bacterial illness [8].

Laboratory findings

A metaanalysis of 25 studies of the diagnostic utility of fecal screening tests as a predictor of a stool culture positive for a known invasive enteropathogen reported the superior performance of fecal lactoferrin over fecal leukocytes or stool occult blood [16]. However, joint maximum sensitivity and specificity, as estimated from summary receiver operating characteristic (ROC) curves were only 86%, 63%, and 68%, respectively. Subsequent studies have indicated that lactoferrin has a sensitivity of 85–93% with a corresponding likelihood ratio positive (LR+) of 4.0–5.5 [17,18] and fecal leukocytes a sensitivity of 57% with LR+ 5.0 (95% CI 2.9–8.8) among outpatients [19]. These studies do not highlight the operational issues

in using these tests in the clinical setting, including need for an experienced microscopist (in the case of fecal leukocytes), need for a fresh specimen (for fecal leukocytes), and integration into clinical care.

Initial work-up should therefore include a fecal lactoferrin measurement or, if microscopy can be performed on a fresh stool sample, presence of fecal leukocytes. If this is positive, a stool culture is indicated as the probability of finding an invasive pathogen is increased and this information is relevant towards further therapy of the patient and is also important from a public health standpoint.

Stool culture

Culture of fresh stool specimens remains the standard for determining an etiologic diagnosis. The rationale for continued use of stool culture includes directed antimicrobial therapy, and assistance with public health goals, such as disease surveillance, identification of outbreaks, further evaluation in cases of suspected inflammatory enteritis, and protection from secondary transmission from ill food service workers [20–22]. The yield of stool cultures in the evaluation of diarrhea in recent travelers is typically below 50% and in the case of community-acquired diarrhea in developed regions this is significantly less (1.5–6%), due to relative increased importance of viral pathogens. Because acute diarrheal disease is often self-limited, and because of the delay in receiving culture results, the contribution of culture results to therapeutic decision-making is often limited. This must be balanced with the need for identification of invasive pathogens and pathogens of public health importance, and also with the need to minimize empiric therapy which may be inappropriate. Most guidelines advise obtaining stool cultures selectively when the patient is moderately or severely ill, in cases with clinical signs of fever, mucus or blood visible in the stool, tenesmus, severe abdominal cramping, or treatment failure [23–25]. For public health reasons, stool cultures should also be tested for specific subpopulations: food handlers, daycare attendees, daycare employees, and any time an outbreak is suspected.

Treatment

Fluid management

Although the goal of fluid management is to reduce morbidity and mortality, most trials of these interventions have assessed other endpoints, such as stool output or need for intravenous rehydration. A direct comparison of intravenous versus oral rehydration has been reported in one small randomized controlled trial (RCT) among 20 adults with cholera and severe dehydration that compared enteral rehydration through a nasogastric tube versus intravenous rehydration [26]. Both groups received initial intravenous fluids. The RCT found no significant difference in the total duration of diarrhea (44 h with IV fluids vs 37 h with nasogastric fluids; difference +7 h, 95% CI −6 to +20 h), total volume of stool passed (8.2 L vs 11.0 L; difference 2.8 L, 95% CI 8 L to +3 L), or duration of *Vibrio* excretion (1.1 days vs 1.4 days; difference 0.3 days, 95% CI 0 to 1 day).

Many subsequent modifications to the formulation of oral rehydration solution (ORS) have been tested in prospective studies. These include amino acid ORS, bicarbonate free ORS, citrate-containing ORS, reduced osmolarity ORS, rice-based solutions [27] and zinc-based solutions [28]. Amino acid-containing ORS were found to reduce the total duration of diarrhea and the total volume of stool in two RCTs [29,30]. Replacing ORS bicarbonate with chloride was not found to be beneficial in one small RCT [31], nor was any significant effect of replacing ORS bicarbonate with citrate found in three RCTs [32–34]. Reduced osmolarity ORS was found to be associated with fewer unscheduled intravenous infusions in a systematic review of trials in children [35]. Fewer trials have examined the efficacy in adults, and among available trials, no consistent effect has been demonstrated. The risk of asymptomatic hyponatremia is higher among those receiving reduced osmolarity ORS in one study (OR 2.1, 95% CI 1.1–4.1) [36], but not in another [37]. The World Health Organization recently changed the formulation of standard oral rehydration solution to a reduced osmolarity formulation [38].

One systematic review (search date 1998, 22 RCTs conducted in Bangladesh, India, Indonesia, Pakistan, Egypt, Mexico, Chile, and Peru) in people with cholera and noncholera diarrhea found that rice-based ORS significantly reduced the 24-h stool volume compared to standard ORS (adults: 4 RCTs, WMD 51 mL/kg, 95% CI 66 mL/kg to 35 mL/kg; children: 5 RCTs, WMD 67 mL/kg, 95% CI 94 mL/kg to 41 mL/kg) [39]. The Cochrane review of this topic has been

withdrawn from the Cochrane Library pending a substantive update.

One RCT found that both rice-based ORS and low sodium rice-based ORS reduced stool output compared with standard ORS (4 L for rice based ORS vs 5 L for standard ORS, $P < 0.02$; 3 L for low sodium rice-based ORS vs 5 L for standard ORS, $P < 0.05$) [40]. A second recent RCT demonstrated shortening of the duration of diarrhea with a starch-based ORS formulation, compared to glucose-based ORS [41]. The addition of zinc to ORS was found to be moderately efficacious in reducing severity of acute diarrhea without increasing vomiting or reducing ORS uptake in a trial in India [42].

Antimicrobial therapy

The use of antibiotics for treatment of domestically acquired diarrhea has been evaluated in at least eleven RCTs comparing one or more antibiotics with placebo or control [43–52]. These trials have evaluated fluoroquinolones ($n = 9$), trimethoprim/sulfamethoxazole (TMP/SMX) ($n = 4$), clioquinol ($n = 1$) (no longer widely used; drug is not available in the United States and available for otic and dermatologic use in several countries), and nifuroxazide ($n = 1$). Six RCTs found that antibiotics reduced illness duration or decreased number of liquid stools at 48 hours, while three RCTs found no benefit in reducing illness duration. One RCT found reduced duration of diarrhea for ciprofloxacin but not for TMP/SMX.

Antibiotics have been extensively investigated for the treatment of traveler's diarrhea. A systematic review [53] and three additional RCTs [54–56] describing the effects of treatment have been reported. The review (search date 1999) compared empirical use of antibiotics versus placebo and found 12 RCTs, among 1474 people with travelers' diarrhea, including students, package tourists, military personnel, and volunteers. Antibiotics evaluated in these trials included aztreonam, bicozamycin, ciprofloxacin, fleroxacin, norfloxacin, ofloxacin, TMP/SMX, and trimethoprim alone. The duration of therapy varied from a single dose to 5 days. The review found that antibiotics significantly increased the cure rate at 72 hours (defined as cessation of unformed stools, or less than one unformed stool per 24 hours without additional symptoms; OR 5.9, 95% CI 4.1–8.6). The additional RCT (598 people, 70% of whom had traveled recently) compared norfloxacin versus placebo. It found that norfloxacin significantly increased the number of people cured after 6 days (34/46 [74%] with norfloxacin vs 18/48 [38%] with placebo; RR 2.0, 95% CI 1.3–3.0).

The systematic review found that the rate of adverse effects varied with each antibiotic, ranging from 2% to 18%. Gastrointestinal, dermatologic, and respiratory symptoms were most frequently reported. The emergence of resistance of the infecting organism to the agent was also documented in a number of the trials. Antimicrobial resistance is clearly of concern for public health. One small RCT included in the review found a significant association between taking ciprofloxacin and isolation of resistant bacteria at 48 hours from these patients' stool samples (ciprofloxacin vs placebo; absolute risk increase [ARI] 50%, 95% CI 15–85%). Another RCT in the review (181 adults with acute diarrhea) reported three cases of continued excretion of *Shigella* in people taking TMP/SMX vs one person taking placebo [57]. Two of these isolates selected for resistance to the drug, although the participants were clinically well. One additional RCT found that people with salmonella infection treated with norfloxacin versus placebo had significantly prolonged excretion of *Salmonella* species (median time to clearance of *Salmonella* species from stool: 50 days with norfloxacin vs 23 days with placebo; CI not provided). In addition, six of nine *Campylobacter* isolates obtained after treatment showed some degree of resistance to norfloxacin.

The continued evolution of antimicrobial resistance among enteropathogens has meant that agents previously found to be effective in clinical trials, such as trimethoprim-sulfamethoxazole or ampicillin, no longer show in vitro activity [58,59]. Further active-control trials, not mentioned above, have evaluated a number of additional candidates, which could be considered. These include aztreonam [60], azithromycin [61–63], and rifaximin [64,65].

Antidiarrheals

A number of antidiarrheal compounds, drugs that generally act by prolonging intestinal transit time through an effect on bowel motility, have been evaluated in clinical trials. These agents include difenoxin, diphenoxylate-atropine [66], lidamidine [67,68], loperamide [68–71], and loperamide-oxide [70–74].

These trials of patients with acute diarrhea have generally been conducted among general practice networks. Trials evaluating loperamide or loperamide oxide have generally used "time to first relief" and "time to complete relief" as endpoints, the latter indicating the time between taking the loading dose and the start of the 24-h period in which no watery or loose stool were passed. The majority of these reports have indicated a benefit of antidiarrheals on symptoms. Some have reported the benefit being experienced in the early phase of the illness, with no impact on total duration of symptoms. The most common adverse effect of these medications is constipation. Two RCTs found that constipation was significantly more frequent in people taking loperamide versus placebo (25% vs 7%; ARI 18%, 95% CI 8–28%; number needed to harm [NNH] 5, 95% CI 3–12 [71]; 22% vs 10.3%; ARI 12%, 95% CI 5–29%; NNH 5, 95% CI 3–18 [70]). Another RCT (230 people) found that symptom scores for tiredness and sleepiness were significantly higher in people taking loperamide oxide 1 mg compared with placebo [73]. Other feared complications such as toxic megacolon have not been reported in clinical trials.

Antisecretory agents

A number of compounds have been developed that modify intestinal fluid secretion and thereby produce a clinical benefit. These include racecadotril, an inhibitor of enkephalinase which prolongs the antisecretory effect of endogenous enkephalins, and octreotide. At least seven trials of racecadotril compared with placebo or another active agent have been reported [75–81]. Placebo-controlled trials indicate that racecadotril shortens the duration of diarrhea. Active controlled trials show similar rates of resolution of symptoms of diarrhea to loperamide, however the rate of constipation is lower following racecadotril compared with loperamide (8.1% for racecadotril 100 mg three times daily vs 31.3% for loperamide 1.33 mg three times daily in one trial) [79]. Octreotide has been reported to shorten the duration of diarrhea due to *Vibrio cholerae* in one small study, although it did not affect the purging rate [82].

Other modalities

Probiotic agents, which are dietary supplements of living commensal microorganisms of low or no pathogenicity, have been proposed as potential therapy for a number of clinical indications [83]. A few small trials of therapy in adults with acute enteric infections have been reported, although the results appear conflicting.

Dietary modification, although frequently recommended for patients with acute diarrheal illnesses, has been evaluated in only small pilot studies, which have not demonstrated additional benefits to patients [84,85].

Supplementation of certain micronutrients has been evaluated as adjunctive therapy in acute diarrhea. The use of zinc supplementation has been extensively evaluated in children although not in adults.

Prognosis

Duration of symptoms

Acute diarrhea in adults is typically self-limited. Among travelers, symptoms typically last 3 to 5 days, may persist for over a week in 8 to 15%, and 2% develop chronic diarrhea [86], although some data suggests that chronic intestinal symptoms may occur more frequently [87,88].

Need for hospitalization

Based on hospital discharge data from the US, approximately 452 000 persons per year were hospitalized with acute diarrhea between 1979 and 1995. This represents $<1\%$ of all cases of diarrhea, and approximately 1.5% of all hospitalizations [89].

Other serious adverse outcomes

One particular concern in those patients with diarrhea due to *Eschericia coli* O157:H7 (EHEC) and other shiga-toxin-producing *E.coli* strains is the development of hemolytic uremic syndrome (HUS), a disorder characterized by hemolytic anemia, thrombocytopenia, and acute renal failure [90]. A recent metaanalysis assessed the risk of HUS after antibiotic treatment of EHEC in nine studies [91]. No association between antibiotic use and HUS were demonstrated (pooled OR 1.04, 95% CI 0.59–1.82). However, the authors reported significant heterogeneity of effect among the studies included in the metaanalysis. As a result, the topic remains controversial, and the value of antibiotics in this setting

remains unresolved, hence the use of antibiotics is not advised [92].

Reactive arthritis and Reiter syndrome are further serious potential complications of enteric infection. The risk of these complications has been documented in the setting of outbreaks of enteric infection with *Salmonella typhimurium* or *S. enteritidis*, *Shigella flexneri*, *Yersinia pseudotuberculosis*, and sporadic cases of *Campylobacter* species or ETEC [93–95]. The prevalence of joint symptoms after infection has been reported to be as high as 37%, although most estimates are in the range of 1–15%. Reiter syndrome usually affects less than 3%. The prevalence of certain high-risk HLA types (such as HLA-B27) in the affected population has generally not been reported, although is clearly relevant to the development of joint symptoms.

Death

Worldwide, death from acute diarrhea remains a major cause of mortality, particularly in children under 5. Mortality trends from diarrhea for the US for the period 1979–87 showed a significant decline in deaths among young children, but rates for those 75 years or older remain around 15 deaths per 100 000 persons. Mortality from dysentery in hospitalized patients in Rwanda in the setting of a nationwide outbreak during the civil war was associated with age less than 5 years or greater than 50 years, severe dehydration on admission (assessed clinically), edema of the legs, and prescription of nalidixic acid (resistance to this agent emerged rapidly during the outbreak) [96,97].

Case presentation 2

A 73-year-old woman with diabetes, which was controlled by diet and oral medication, was admitted to the intensive care service of a hospital after she was admitted 10 days earlier with a clinical picture of community-acquired pneumonia. She had been admitted with high fever up to 40°C, had an elevated peripheral white blood cell count of 14.5×10^9/L without bands, and had dyspnea requiring oxygen support of 4 L/minute O_2 by face mask. She was started on a sliding scale of insulin to control moderate hyperglycemic values. Her condition did not require intubation, and she was started on antibiotics (a third-generation cephalosporin with a respiratory fluoroquinolone), intravenous fluids and nonsteroidal medication for fever upon admission. A chest radiograph taken on admission showed a left lower lobe infiltrate.

She gradually improved: she had defervesced on day 5 and was coughing less. Her blood sugars normalized without additional insulin and she was markedly less dyspneic by day 7. Her WBC count had also normalized by the 5th day, and the chest radiograph showed a similar but perhaps more dense lung infiltrate in the same area of the left lower lobe. On day 8 she developed watery offensive diarrhea with severe abdominal cramping. She was anorexic and hypoglycemic. Her temperature increased to 38.5°C, her heart rate increased to 135 beats/minute, she became hypotensive, and on her peripheral blood smear she had 22.4×10^9 WBC/L with 15% bands. Given her worsening clinical picture, she was transferred to the intensive care unit.

Diagnosis

Epidemiology

Diarrhea occurring during hospitalization may be due to a number of infectious or noninfectious causes. The leading cause of infectious nosocomial diarrhea is cytotoxin-producing *Clostridium difficile*. Other infectious pathogens account for only a small proportion of nosocomial diarrhea, but may be important in outbreak settings. The patient population and locally prevalent pathogens are additional influences on the spectrum of pathogenic organisms encountered. Antibiotic-associated diarrhea may be caused not only by disruption of normal intestinal flora, but also by overgrowth of pathogenic organisms such as *C. difficile*. The effects of the antibiotic may be directly on the intestinal mucosa, gastrointestinal motility, or mediated through alteration of colonic metabolism induced through changes in the normal resident bacterial flora [98].

The rates of nosocomial diarrhea vary, in part due to the definition of diarrhea; rates of above 30% of admission have been reported [99]. Among a large cohort of antibiotic-treated hospitalized patients, the frequency of diarrhea was 12% [100]. *C. difficile* accounts for approximately 25% of cases

of antibiotic-associated diarrhea [100,101]. Risk factors for *C. difficile* symptomatic infection include advanced age, length of hospitalization, and antibiotic use [102,103]. Proton pump inhibitors have been associated with increased risk for community-acquired *C. difficile*-associated diarrhea [104].

Clinical findings

Clinical findings often start shortly after use of an antibiotic although a delayed onset of up to 8 weeks is possible. Most patients have foul-smelling, watery, greenish diarrhea, the presence of mucus and blood in the stool, with signs of focal abdominal tenderness or tenesmus often present. However, milder presentations without diarrhea occur, and fulminant colitis is estimated to occur in 1–3% of cases [101]. Leukocytosis is common, and may even be markedly elevated [105].

Stool culture

A widely used policy in microbiology laboratories is to reject stool specimens obtained more than 3 days after admission (the "three-day rule"). The rationale for this is illustrated by the difference in stool culture yield for specimens taken $<$72 hours after admission compared with specimens taken 72 hours or more after admission: 3.3% vs 0.5% [106]. A recent prospective study to derive guidelines for stool culture of inpatients proposed a modification to the three-day rule, suggesting that cultures be obtained in the case of nosocomial diarrhea ($>$72 hours after admission) if at least one of the following criteria are met: age $\geqslant$65 years, HIV infection, neutropenia, or a nosocomial outbreak suspected. This would have resulted in only two missed positive cultures for enteropathogens (other than *C. difficile*) of 65 positive cultures from over 27 000 stool cultures obtained in three hospitals over a cumulative period of 14 years. The rule would have led to a reduction in workload for the microbiology laboratory of between 47% and 62% in these hospitals. The detection of nosocomial outbreaks may have been delayed in some instances, especially if cases were widely distributed across hospital wards.

Identification of *C. difficile* in a stool culture is not sufficient as strains that do not produce toxins are not pathogenic, and the presence of one or both of the toxins must be established. In addition, isolation of *C. difficile* may take 48–72 hours, which delays the diagnosis. Some strains of *C. difficile* have been associated with higher virulence leading to increased morbidity and mortality; in particular the strains BI, NAP1 or ribotype 027 – which are all synonymous – have been observed to lead to disease that is more severe, more prolonged, more refractory to therapy, and more likely to relapse [107–109].

Special examinations

The use of stool biomarkers has been examined as an aid to identification of patients with a higher likelihood of positive tests for *C. difficile*. The odds of a positive stool cytotoxin assay in persons with positive tests for stool leukocytes have been reported to be increased, whether detection is by lactoferrin assay (OR 3.7, 95% CI 1.8–7.8) or by light microscopy (OR 2.4, 95% CI 1.1–5.4) [110]. Both have imperfect sensitivity, although stool microscopy may be the less sensitive screening test [19,111].

The gold standard test is a cell culture-based cytotoxin assay, which takes 24 to 48 hours. The impetus for alternative diagnostic tests has been the diagnostic delay and requirement for a tissue culture facility. A variety of rapid assays have been developed to address these needs. Enzyme immunoassays (EIA) have been developed for toxin A and B, or the combination of both, with reduced sensitivity (72–94% compared with tissue culture), but results are available in a few hours [112]. If the initial test is negative and diarrhea persists, a second or even a third sample should be evaluated to compensate for limited sensitivity. The combined toxin A/B tests have superior sensitivity to EIAs that test for toxin A alone, possibly owing to the detection of toxin A−/B+ strains [113]. Realtime PCR on toxin B and immunochromatography assays on toxin A and B have some potential as rapid screening tests but are not better than the gold standard cytotoxicity test; use of PCR remains limited [114,115]. The use of latex agglutination assays that detect glutamate dehydrogenase has been discouraged by the Society for Healthcare Epidemiology in America because of the low sensitivity of the test, despite the ease of performance of the test, low cost, and high specificity [112]. Radiographic studies lack both sensitivity and specificity but toxic megacolon or thumbprinting can be suggestive of infection with *C. difficile*. Abdominal computed tomography scanning typically shows thickening of the mucosa, yet this is not a pathognomonic sign [116,117].

When a diagnosis needs to be made more rapidly, flexible sigmoidoscopy should be considered. This is particularly useful in situations where ileus has developed and stool studies cannot be obtained. In severe cases, pseudomembranous colitis may be visualized on examination. The typical appearance is of yellow adherent plaques about 10 mm in diameter scattered over the colonic mucosa and separated by hyperemic areas. Biopsies of the area show plentiful neutrophils in a classic "volcano" exudate of fibrin. About 10% of the cases of pseudomembranous colitis are in the proximal parts of the colon and can be visualized by a full colonoscopy.

Treatment

Usual interventions that are applicable to the management of diarrhea in other settings, such as correction of volume deficits and electrolyte imbalance, are important. Beyond this, the first consideration in therapy is to stop the offending antibiotic, whenever possible. This will often be sufficient to resolve the symptoms promptly. If the antibiotic needs to be continued or if symptoms are more severe, antibiotic therapy can be considered. Several effective therapies are available including vancomycin, teicoplanin, fusidic acid, metronidazole, and bacitracin [118–120]. Even though the efficacy of several antibiotics is similar [121,122], it did appear that oral vancomycin was superior in one small placebo-controlled trial [123]; the drug of choice is metronidazole 500 mg orally three times daily for 10–14 days, as it is recommended that vancomycin use be restricted where possible [112]. Where available, teicoplanin might be a good first choice [123]. Metronidazole failure could possibly be attributed to a slower and less consistent microbiologic response [124]. Sometimes longer therapy is required, particularly when the offending antibiotic is still given. When therapy is needed, patients usually improve within 72 hours of the first dose of metronidazole. Vancomycin given orally at a dose of 125 mg four times daily is effective [125] but, due to its higher cost and because of efforts to limit the spread of vancomycin-resistant organisms, metronidazole is preferred. Vancomycin can be considered for patients who have not responded to at least two courses of metronidazole, patients with allergies or intolerance to metronidazole, pregnant women, and children. If there is no adequate clinical response, the oral dose of vancomycin can be increased to 500 mg orally four times daily. For patients who are toxic or unable to take oral medication and in absence of a feeding tube, intravenous metronidazole at a dose of 500 to 750 mg every 6 hours can be used, although intravenous therapy is inferior and parenteral vancomycin is ineffective. Alternatives are under further study. Linezolid shows in vitro sensitivity but needs further clinical testing. Antimotility agents (e.g. loperamide, etc.) are contraindicated. Tolevamer, a polymer that binds the toxins, seems effective in mild to moderate cases and is under development [126]. Fusidic acid has been reported to be as effective as metronidazole [127].

Relapses can occur in up to 20% despite appropriate therapy. Reinfection can also occur. A second course of metronidazole is usually sufficient but prolonged courses of vancomycin can be considered in the face of multiple relapses with clinical signs, e.g., oral vancomycin courses followed by a slow taper over 6 weeks [128]. Use of probiotics with, e.g., *Saccharomyces boulardii* may be useful, although the evidence remains equivocal [129–132]. Historically, fecal enemas from healthy donors have been tried in an effort to restore normal healthy bowel flora in an effort to competitively displace enteric pathogens [133]. In a small study, serial therapy with vancomycin and rifaximin was given in persistent recurrent *C. difficile*-associated diarrhea episodes with success in terminating recurrent symptoms in 7 out of 8 cases [134].

Case presentation 3

A 27-year-old man is seen in the outpatient department for symptoms of diarrhea over the last 3 months. He reports stools every 2–3 hours that are watery or consist of poorly digested food he had consumed over the previous day. Occasionally the stool has an oily consistency. He has noted no fever, blood in the stool, tenesmus, or other abdominal complaints. He is known to be HIV-positive, although had declined close monitoring of his immune and virologic status, and has not been receiving antiretroviral therapy. He is taking no regular medications apart from multivitamins and a herbal supplement. He has not traveled recently, has not been sexually active for several months preceding the onset of symptoms, and has no pets.

continued

Case presentation 3 (continued)

On examination he is afebrile, with stable vital signs. His abdominal examination is unremarkable. His laboratory studies disclose: sodium 137 mmol/L, potassium 3.6 mmol/L, urea 3.6 mmol/L (10 mg/dL), creatinine 71 μmol/L (0.8 mg/dL), and CD4+ T-lymphocyte count 27 × 10^6/L (27 cells/μL).

Diagnosis

Epidemiology

Chronic diarrhea is a heterogeneous illness, encompassing symptoms caused by infection, inflammatory bowel disease, functional bowel syndromes, malabsorption, and other idiopathic syndromes. A consequence of this heterogeneity is a complex epidemiology, which remains relatively poorly defined. Methodologic flaws in the criteria for assembly of study cohorts, definition of diarrhea, and definition of "chronic" may all be important. The age- and sex-adjusted prevalence of this symptom have been estimated at 6.0 cases per 100 persons (95% CI 4.4–7.7) [135–139].

Persons infected with the human immunodeficiency virus (HIV) are commonly affected by diarrhea. The incidence of chronic diarrhea among participants in the Swiss HIV Cohort study was 8.5 per 100 person-years (95% CI 7.4–9.9) between July 1992 and June 1994, and 9.1 (95% CI 7.8–10.7) between July 1994 and March 1996 [140]. Among participants in the Adult/Adolescent Spectrum of HIV Disease study, conducted in the US, the incidence of diarrhea caused by bacterial pathogens known to be causes of enteric illness was 7.2 cases per 1000 person-years between 1992 and 2002 [141]. This is likely to represent a minimal estimate, given the study design. In this same study the most commonly identified bacterial cause of diarrhea was *C. difficile*, with the highest incidence rates in the most severely immunosuppressed symptomatic AIDS patients [127]. Prior studies have demonstrated that the risk of chronic diarrhea is related to degree of immunosuppression [141–143], transmission category [142], receipt of antiretroviral therapy [140,144], or prophylaxis against opportunistic infections [145,146].

Clinical findings

Limited data are available regarding the utility of physical findings for making an etiologic diagnosis in patients presenting with chronic diarrhea. Among HIV-infected patients, the history and physical examination have been reported not to be helpful in determining whether or not an enteropathogen will be identified [147], with the exception that abdominal tenderness was commoner in patients with CMV [148]. The American Gastroenterological Association have recommended that complete evaluation of persons seeking care for chronic diarrhea include evaluation of fluid balance, nutritional status, presence of flushing or rashes, mouth ulcers, thyroid masses, wheezing, arthritis, cardiac murmurs, hepatomegaly, abdominal masses, ascites, and edema. Attention should be paid during anorectal examination to the anal sphincter tone and the presence of perianal fistula or abscess [137].

Stool culture

The utility of stool studies for detection of enteric pathogens is well documented for the evaluation of chronic diarrhea in HIV infection. The yield of stool studies (including culture for enteric bacteria and mycobacteria, and microscopy for parasite ova) varies depending on the patient characteristics of the study population and the intensity of the diagnostic evaluation (Table 8.2).

Recommendations regarding the most appropriate diagnostic strategy for patients infected with HIV have not been formally tested in prospective studies examining a broad range of outcomes, including quality of life. Strategies range from an intensive work-up, including upper endoscopy and colonoscopy with mucosal biopsy, to a minimal evaluation involving only stool cultures [149]. The American Gastroenterological Association guidelines, published in 1996, propose a stepwise approach, which may be modified according to the clinical judgement of the physician [150]. The initial step identifies enteric bacteria and parasites through stool studies. Three samples should be submitted initially.

Laboratory tests

The use of fecal biomarkers as screening tools to detect gastrointestinal pathology have not been extensively evaluated in the setting of chronic diarrhea. The prototypic biomarker, occult blood, has not been extensively validated as a marker of intestinal

Table 8.2 Prevalence of enteric pathogens causing diarrhea in HIV-infected patients

Reference	N (%)†	Evaluation‡	Prevalence of pathogens		Pathogens§
			Patients with diarrhea (%)	Patients without diarrhea (%)	
Dworkin [162]	22 (55)	Stools	75	10	MAC *Cryptosporidia*
Laughon [163]	77 (64)	Stools	50	11	*Cryptosporidia* *Campylobacter* species
Smith [164]	30 (67)	Stools, EGD, colonoscopy	85	10	CMV *Entamoeba histolytica*
Antony [165]	66 (100)	Stools	55	–	MAC CMV
Rene [166]	132 (52)	Stools, EGD, colonoscopy	59	28	*Cryptosporidia* CMV
Cotte [167]	81 (73)	Stools	64	15	*Cryptosporidia* CMV
Kotler [168]	194 (73)	Stools	83	2	*Microsporidia* *Cryptosporidia*
Blanshard [148]	155 (100)	Stools, EGD, sigmoidoscopy	83	–	*Cryptosporidia* *Microsporidia*
Prasad [169]	59 (44)	Stools	73*	–	*Isospora Cryptosporidia*
Manatsathit [161]	45 (100)	Stools, EGD, colonoscopy	64		*Cryptosporidia* Tuberculosis

Adapted from references [150] and [161].
† Number of patients studied and proportion with diarrhea (%).
‡ Endoscopic procedures listed only if performed in all patients.
§ Two most common organisms are listed.
* Prevalence of pathogens not reported separately for patients with and without diarrhea.

inflammation in chronic diarrhea. When compared to another biomarker, the leukocyte-derived protein calprotectin, against a criterion standard of direct visualization at colonoscopy with biopsy among patients undergoing evaluation for chronic diarrhea of unknown cause or chronic colitis of unknown activity, fecal hemoglobin was of poor discriminatory value for the presence of intestinal inflammation (area under ROC curve (AUC) = 0.58, 95% CI 0.46–0.70) [151]. Fecal calprotectin levels were elevated and significantly associated with the presence of intestinal inflammation (AUC 0.89, 95% CI 0.81–0.97). Fecal lactoferrin, another leukocyte-derived protein, was reported to have sensitivity of 90%, specificity of 98%, positive predictive value (PPV) 82%, and negative predictive value (NPV) 99% for ulcerative colitis and Crohn's disease in patients being investigated for chronic diarrhea with biomarkers and "an extensive evaluation" that included endoscopy [152].

Treatment

Antimicrobial therapy

Given the broad differential diagnosis, empiric antimicrobial therapy without initial evaluation is not recommended in this population. If no enteric pathogens are identified on stool studies, an empiric course of oral antibiotics may be considered. This may include a fluoroquinolone or a macrolide. Antiprotozoal therapy can also be considered such as empiric use of trimethoprim-sulfamethoxazole if *Cyclospora* or *Isospora* infections are suspected. Empiric use of metronidazole is indicated when the suspected pathogens include *Giardia lamblia* or *Entamoeba histolytica*, and

Table 8.3 Special pathogens and therapy

Cyclospora	TMP/SMX* 800 mg/160 mg twice daily × 7 d
Isospora	TMP/SMX 800 mg/160 mg twice daily × 10 d None (self-limited disease in immunocompetent host)
Cryptosporidium	In AIDS patients: Nitazoxanide plus antiretroviral therapy
Giardia	Metronidazole 250 mg three times daily × 5 d Tinidazole 2000 mg daily × 1 d Quinacrine 100 mg three times daily × 7 d Furazolidone 100 mg four times daily × 7–10 d Albendazole 400 mg daily × 7 d
Entamoeba	Metronidazole 250 mg four times daily × 7 d
MAC	Ethambutol and clarithromycin
HSV	Acyclovir
HIV	Antiretroviral combination therapy
CMV	Ganciclovir Valganciclovir

* Trimethoprim-sulfamethoxazole.

would also be of benefit in cases of *Clostridium difficile* colitis. Directed therapy may be available against identified pathogens (Table 8.3). Treatment of cryptosporidiosis in a normal host is typically not necessary, as this is a self-limiting disease; although a high clearance rate from stools has been reported with use of nitazoxanide and paromomycin. Use of nitazoxanide in HIV-positive subjects can be considered, even though effectiveness has not been proven [153].

Antidiarrheals

Nonspecific treatment with antidiarrheals, such as loperamide, loperamide oxide, diphenoxylate-atropine, codeine, or tincture of opium, may be considered for empirical therapy. The situations in which such use is tenable include: as a temporizing measure prior to a planned diagnostic evaluation; if diagnostic evaluation does not identify a specific etiology; if a diagnosis is made for which no effective therapy is known or for which specific treatment fails [138]. Antidiarrheals may also be considered in HIV-infected persons who have nonbloody diarrhea and a negative initial evaluation on stool testing, although these recommendations have not been evaluated in prospective studies [150].

The somatostatin analog octreotide has been evaluated as a potential therapy for HIV-associated diarrhea, but has not been found to be superior to placebo [154].

Other therapy

The evidence for the efficacy of probiotic agents in chronic diarrhea is limited. Dietary modifications, such as a diet based on medium chain triglycerides, have been evaluated as adjunctive therapy in HIV-infected patients with chronic diarrhea, and may be of value [155]. Use of moderate amounts of lactose-containing products does not appear to worsen symptoms of diarrhea [156]. Zinc does not reduce the proportion of patients with chronic diarrhea after 2 weeks of supplementation, although the evidence from one study is limited by high rates of loss to follow-up, perhaps reflecting, in part, a lack of efficacy or poor tolerability of the supplement [157].

Prognosis

Duration of symptoms

Remission rates of chronic diarrhea have been estimated to be 282 per 1000 person-years [135]. Given a similar incidence rate, the overall prevalence of chronic diarrhea was stable in the survey.

Survival

Chronic diarrhea among HIV-infected persons in the Swiss HIV Cohort study was found to be an independent predictor of death (risk ratio 1.5, 95% CI 1.2–1.8) [140].

Glossary

(per definitions used in Infectious Diseases Society of America guidelines)

Acute diarrhea: Diarrheal episode lasting less than 14 days.

Chronic diarrhea: Diarrheal episode lasting more than 30 days.

Diarrhea: Alteration of normal bowel movement, associated with increase in stool volume or water content or frequency. Also decreased stool consistency (unformed or liquid stools).

Infectious diarrhea: Diarrheal episode due to infection with an enteropathogenic organism.

Persistent diarrhea: Diarrheal episode lasting more than 14 days.

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CHAPTER 9
Urinary tract infections

Thomas Fekete

Case presentation 1

A 35-year-old woman is seen in the outpatient clinic for a 2-day history of worsening urinary burning and frequency. She is a healthy woman with no medical problems. She has two children at home and is currently using oral contraceptives. She recalls a urinary tract infection (UTI) from about 6 years earlier that responded to a 3-day course of antibiotics, and she has had no sequelae of UTI since. She has no symptoms of vaginal itching or discharge. On examination she looks mildly uncomfortable but otherwise in no distress. She is afebrile and has normal vital signs. There is no costovertebral angle tenderness. There is slight discomfort with deep palpation over the pubis, but the bladder is not enlarged. The patient refuses a pelvic examination since she has just seen her gynecologist 2 weeks earlier for a routine check-up and was told everything was normal.

UTIs are a common medical problem, with costs estimated at more than US$1.6 billion in 1995 in the United States [1]. While many people with serious underlying illnesses develop UTIs in healthcare facilities as a consequence of bladder dysfunction and catheterization, women are especially vulnerable to getting UTIs even in the absence of underlying illness. About 40% of adult women report having had a previous UTI [2]. In young, sexually active women the rate of UTIs has been reported to be as high as 0.5 episodes per woman year [3]. Moreover, in a random telephone dialing survey, nearly 11% of women reported at least one UTI in the past 12 months [1]. For the more specific diagnosis of pyelonephritis, the estimated annual population based rate was 15–17 per 10 000 for women and 4–6 per 10 000 for men [4]. The incidence of all these urinary infections has been stable for the past 15 years.

Case presentation 1 (continued)

Urine dipstick testing is done in the office. It is strongly positive for leukocyte esterase and nitrites but negative for blood, protein, and glucose. Is there sufficient evidence to make a clinical diagnosis of UTI in this patient?

Diagnosis

In the case presentation, this woman has a short history of dysuria and frequency with no prior known urinary pathology. A systematic review assessing the accuracy of history-taking and physical examination for diagnosing acute uncomplicated UTI in women reveals that dysuria and frequency without vaginal discharge or irritation raises the probability of UTI from about 48% to more than 90% [5]. While a positive urine dipstick can raise this probability even higher, a negative result will still leave a high post-test probability of UTI. The clinical elements in our patient (dysuria, frequency) along with history of hematuria, back pain, and costovertebral angle tenderness all tend to increase the likelihood that the woman has a UTI, as do the lack of vaginal complaints (discharge, irritation). Since the pretest

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Table 9.1 Likelihood ratios (LR) for some important UTI clinical features

Clinical features	Positive LR	Negative LR
Dysuria	1.5	0.5
Frequency	1.8	–
Hematuria	2.0	–
Vaginal discharge	0.3	–
Vaginal irritation	0.2	–
Back pain	1.6	0.8
Vaginal discharge on examination	0.7	–
Costovertebral angle tenderness	1.7	–

probability of UTI in an otherwise healthy woman coming to the clinic with a suspicion of UTI is so high (48%), it would be a fair question to ask how low a probability would argue against the initiation of therapy. The study made a formal evaluation of clinical features of UTI by a systematic review of the literature (464 articles) and focused on nine that met rigorous inclusion criteria. These individual studies were chosen because they allowed an assessment of individual features such as dysuria or vaginal irritation so that each one could be given a likelihood ratio for the presence of a UTI. This likelihood ratio could be applied to a prior probability of UTI (as determined by the patient or the physician) so that a reasonable clinical diagnosis could be made. The likelihood ratios for some of the most important clinical features (where the 95% CI did not include 1.0) are in Table 9.1.

The two most common tests used on the commercial dipstick to assess possible UTI are the nitrite (nitrate reductase) and the leukocyte esterase tests [6]. The nitrite test measures the presence of the enzyme nitrate reductase – a bacterial enzyme present in many though not all gram-negative bacteria. False positives are rare, but the rate of false negatives ranges from 10% to 30% and is especially high in infections caused by nitrite-negative organisms, when the urine has a low pH or a large amount of urobilinogen or ascorbic acid. Leukocyte esterase measures the presence of white blood cells in the urine. While other conditions can cause pyuria, the clinical setting is usually sufficiently clear to rule out these infections. False-negative results can be found with low concentrations of urinary leukocytes, the presence of ascorbic acid, phenazopyridine, or large amounts of protein. One of the problems of these rapid tests for UTI is that they are affected by spectrum bias [7]. What this means is that the sensitivity of the test is influenced by the underlying characteristics of the population being studied. In this example, the sensitivity of a positive dipstick test was 0.92 (95% CI 0.82–0.98) whereas, if the prior probability was low, the sensitivity would be reduced to 0.56 (0.03–0.79). When the presence of a positive urine culture is used as the reference standard of a UTI, the performance characteristics of various components of the urinalysis can be disappointing [8]. The clinical benefit of treatment for symptomatic women with a negative dipstick test in the absence of cultures has been evaluated in a double-blind randomized controlled trial. Suitable women with negative nitrite and leukocyte esterase dipstick tests were randomized to a 3-day course of trimethoprim vs placebo [9]. The speed and degree of improved dysuria strongly favored the trimethoprim-treated patients suggesting an infectious entity despite negative screening tests (and no urine culture). This result would not be expected given a systematic review of dipstick testing that indicates negative dipstick results have the capacity to rule out even low levels (about 10^2) of bacteriuria [10]. Perhaps using cultures as the marker for likelihood of improvement in this setting misses some people destined to respond clinically to antibiotics.

In terms of noninvasive diagnostic tests that can be done in the ambulatory setting, there are two options: microscopic analysis of the urinary sediment and urine culture. Urine microscopy (determining in a semiquantitative manner the concentration of leukocytes in the urine) is done as a routine part of the urinalysis in many hospital laboratories, but the urine dipstick is almost as reliable in confirming UTI as the microscopic analysis [11] and is quicker and less expensive than microscopy. Both tests are imperfect but, in an Emergency Room study, each test had roughly the same number of false negatives and false positives when compared with the results of urine culture [12]. In pregnancy, the urine culture is the test of choice, since even a negative urinalysis does not ablate the need for culture. Less is known about the usefulness of dipstick testing in hospitalized patients, who experience higher rates of pyuria and UTI than

ambulatory patients. Zaman and colleagues found high specificity using >10 WBC/μL and >5 WBC/μL (94% and 90%), but lower sensitivity with these values (57% and 84% respectively) [13]. The positive predictive values were 91% and 77% and the negative predictive values were 68% and 93%, respectively. Quantitative determination of pyuria in uncentrifuged urine (as contrasted with the usual semiquantitative assessment of WBC in centrifuged urine) can be a useful tool for research [11] to assure a consistent definition of UTI, but it is time-consuming and rarely done. Gram stain of uncentrifuged urine is a test seldom done in most clinical laboratories, but when positive, it has positive likelihood ratios of 7.0 and 8.1 for confirming the presence of infection by gram-positive cocci and gram-negative rods, respectively [14].

A management strategy that does not include any kind of urine testing might be appealing as a way of reducing costs and perhaps avoiding clinic visits. Unfortunately, this could result in considerable overtreatment. In a cohort of 231 Canadian women presenting with dysuria, about 80% thought that they had a UTI [15]. Physician diagnosis of a UTI occurred in 92% of cases; however, UTIs were documented in only 53%. As a result, unnecessary antibiotics were frequently prescribed. Combining clinical features and urine testing for pyuria and nitrates could have reduced the number of unnecessary treatment courses considerably. Unfortunately, it would have delayed the treatment of infection in a number of women with true cystitis (positive urine culture but negative dipstick test). The lesson from this set of observations is that, in the case of a very common problem like UTI, there can be diagnostic uncertainty comparable to that of other problems seen in the ambulatory setting. The careful clinician might interpret this as a choice between overtreatment and overdiagnosis. Luckily the consequences of either approach are modest both economically (since the drugs and the diagnostic tests are fairly inexpensive) and in toxicity (since the medications are well tolerated and a short delay in the treatment of UTI almost never leads to serious sequelae). The McIsaac paper algorithm led to a reduction in unnecessary antibiotic use from 40% of all drugs used to 27%, and a reduction in total urine cultures obtained from 87% to 40%; however, it also led to a reduction in the sensitivity for UTI from 92% to 81%. These guidelines would result in one delay of therapy in every 13 women with UTI.

Treatment guidelines for telephone-based prescription strategies might have the same problem of overtreatment. In a large study of women in the Group Health Cooperative in Washington state, who stated on the telephone that they had dysuria and met certain clinical criteria, the use of nurse prescribers of antibiotics resulted in very few clinic visits for UTI [16]. Sparing office visits might be cost-effective even at the expense of excess antibiotic prescriptions.

By strict definition, a UTI should have $>10^3$ colony forming units of microbe per mL of urine [17], but urine cultures demand time for processing and growth (at least 18 hours) and further time for identification of the microbe and determination of antimicrobial susceptibility. A treatment delay while these results are awaited can increase the morbidity of UTI, and the culture itself increases the cost of diagnosis. However, there are no RCTs that have randomized patients with presenting UTI symptoms to urine culture versus no culture.

Obtaining urine cultures in patients who require hospitalization, who are allergic to first-line antibiotics, or who fail therapy is done in anticipation of possible changes in treatment based on resistance or drug intolerance. Severely ill patients may also benefit from a urine culture insofar as it might guide appropriate changes in treatment if there is a failure to respond to initial therapy. Withholding treatment until a culture report is available is reasonable only for those patients with a low suspicion of infection or significant drug allergy. The only benefit of obtaining a culture when there is a plan to initiate treatment is to help interpret treatment failure. In most studies to date of healthy ambulatory women, this is rare (<5%) but changing resistance patterns could affect this strategy [18].

Other diagnostic testing

UTI can be defined as simple or complicated based on the respective absence or presence of documented or suspected structural or physiologic abnormalities of the urinary tract. There is no information in Case 1 to suggest abnormal urinary anatomy and physiology and thus no need for radiological localization of the infection [19].

Case presentation 1 (continued)

After checking to make sure the patient had no drug allergies, the physician prescribed a 3-day course of trimethoprim-sulfamethoxazole (TMP-SMX) (160/800 mg orally twice a day). A phone call to the patient 2 days after the completion of therapy showed that her symptoms were totally resolved and that she had experienced only mild nausea on antimicrobial therapy.

Therapy for the ambulatory patient

The results of urine cultures in ambulatory patients with UTIs show a great preponderance for *Escherichia coli*. Although *E. coli* is a common commensal of the gastrointestinal tract, the strains that cause UTIs are a subset of gastrointestinal-adapted strains that are also able to adhere to the periurethral area and to the cells lining the urinary tract. Similarly other gram-negative bacteria (such as *Klebsiella* spp., *Proteus* spp.) with uropathogenic attributes can also cause UTIs in otherwise healthy people.

There are two important gram-positive uropathogens of ambulatory women. The first is *Staphylococcus saprophyticus*, a coagulase-negative staphylococcus present in young women especially during the summer months. The gene sequence of *S. saprophyticus* has revealed differences from *S. aureus* and *S. epidermidis* that favor survival of *S. saprophyticus* in the uroepithelial environment [20]. These include enhanced adherence to bladder cells, adaptive ion transport pathways (to adapt to varied urinary ion concentrations) and the elaboration of urease. The second gram-positive pathogen, *Enterococcus*, is the third most common genus after *Escherichia* and *Klebsiella* and tends to cause infection in people who have received antibiotics previously.

The threshold concentration of organisms in the urine distinguishing contamination from infection has been the source of some disagreement in the past. While quantitative cultures usually show a large number of organisms present ($>10^5$/mL), about 25–30% of UTIs will have fewer organisms ($>10^3$/mL) [21].

There are many choices of antimicrobials for the treatment of UTIs and a number of potential treatment durations. The patient in Case 1 had resolution of symptoms of her first UTI after a 3-day course of therapy. An older approach, single-dose treatment, has a higher failure rate and early recurrence as compared to short-course (usually 3-day) treatments [22,23]. A systematic review of the relative efficacy of single-dose versus 3-day or longer therapy shows better outcomes with the 3-day or longer therapy. The question of whether prolonged treatment (a week of more) is superior to 3-day therapy has been addressed in a systematic review [24]. Unsurprisingly, in the management of uncomplicated cystitis in women, 3-day courses have fewer side effects but slightly inferior bacteriologic efficacy as compared to prolonged courses. The symptomatic clinical response is indistinguishable in the individual studies as well as in the combined analysis ($n = 5000$) so there is no compelling reason to use more expensive and potentially toxic durations of antibiotic treatment for uncomplicated cystitis.

Studies of single-dose therapy using β-lactams, TMP, TMP-SMX, and fluoroquinolones have essentially been halted, not only because the clinical outcomes are worse, but also because the total costs (including time off from work, repeated visits to healthcare providers, etc.) are magnified by relatively small differences in the recurrence rate [25,26]. The only drug still given in a single dose is fosfomycin which has a long half-life (5.7 hours) and high urinary levels (a single 3 g dose is given as a sachet dissolved in water) [27]. The use of single-dose fosfomycin or longer courses of nitrofurantoin (5–7 days) gives a more reduced cure rate than TMP-SMX or fluoroquinolones [25,28–30]. Therefore these agents find their greatest use in salvage regimens or when patients have significant drug allergies or intolerance. Furthermore, fosfomycin (about US$38 in 2007) and nitrofurantoin (about US$27 in 2007) are more expensive than generic trimethoprim-sulfamethoxazole or ciprofloxacin [31].

Numerous studies have demonstrated the inferiority of β-lactams for UTI [25,32]. That is not to say that some patients do not respond well to inexpensive β-lactams such as amoxicillin but that the overall rates of response and relapse are disappointing as compared with other drugs even in the absence of β-lactam resistance in uropathogens. Thus expanding the β-lactam spectrum by using amoxicillin/clavulanate does not provide robust initial improvement

or prevention of recurrence. A randomized trial of 3-day regimens of amoxicillin/clavulanate or ciprofloxacin showed a clinical cure rate of 58% for the β-lactam and 77% for ciprofloxacin ($P < 0.001$) [33]. Surprisingly, the durability of response seemed equal regardless of the initial susceptibility of the organism to amoxicillin/clavulanate. The authors speculate that a large share of failure is attributable to a failure to eradicate the organism from the genitals (45% vs 10% persistent colonization respectively). However, β-lactams are recommended for the treatment of UTI during pregnancy given their favorable safety profile and the concerns about toxicity for the alternative first-line agents.

It is important to interpret the results of clinical trials of antimicrobial agents for UTIs in the context of the local antimicrobial resistance patterns. Changing patterns of resistance of uropathogens occur constantly [34]. Therefore, changes in strains and resistance patterns of bacteria causing UTI, as well as differences in dosages of antimicrobials used, make the interpretation of older studies challenging. An example is a large, well-designed study comparing the outcome of treatment with either ciprofloxacin, ofloxacin, or TMP-SMX in women with UTI [18]. Although a large number of women were in this study (866 were recruited and 688 were available for analysis), there were no significant differences among the three study drugs in terms of outcome or adverse reactions. The study was powered to show significance assuming a success rate of 93% for ciprofloxacin, 80% for TMP-SMX, and 90% for ofloxacin. The actual clinical success rates were 93% for ciprofloxacin, 95% for TMP-SMX, and 96% for ofloxacin. Of note, the patient outcomes were as good as or better than expected (bacteriologic responses of 92–97% and clinical responses of 93–96%). Resistance to any of the drugs used was quite low; therefore the results may not apply in situations where resistance to one or more of the drugs is higher. In that situation, the outcome might be less good with the drug to which resistance has now emerged. Finally, the overall "better-than-expected" outcome might reflect especially mild disease in the patients enrolled in this study – thus true differences in outcome (or even adverse events) might be underestimated as compared with a sicker population with less capacity for spontaneous or aided recovery. A Cochrane review about fluoroquinolones for uncomplicated cystitis in women indicates that, although as a class fluoroquinolones have shown good clinical outcomes in the published literature, there might be clinically important differences in efficacy and tolerability within the class or compared with other agents [35].

As drug resistance patterns change, it is important to identify predictors of resistance to avoid ineffective empiric therapy. A study from the San Francisco bay area showed that recurrent UTI and prior fluoroquinolone use were strong predictors for fluoroquinolone resistance (OR of 8.1 and 30.4, respectively) [36]. This study also indicated that 92% of the ciprofloxacin-resistant strains were also TMP/SMX resistant. A large study looking at nearly 2000 ciprofloxacin-resistant strains of *E. coli* obtained in 2004–5 from outpatient urine cultures from 40 North American medical centers showed that isolated fluoroquinolone resistance was present in only 10% [37]. Cross-resistance to ampicillin and TMP/SMX was common; resistance to cefdinir and nitrofurantoin was much less common. Resistance is even more of a problem in long-term care facilities where prior fluoroquinolone use and urinary catheterization were strongly associated with fluoroquinolone resistance with odds ratios of 22 and 19, respectively [38]. The use of fluoroquinolones seems to have a short-term effect on the acquisition of fluoroquinolone-resistant UTI pathogens, but an Italian study showed that the odds ratio of having a ciprofloxacin-resistant *E. coli* was 20 in the first month after a course of fluoroquinolones, 7.2 for the next 2 months and 3.3 for the next 3 months [39].

A potential limitation of guidelines is that they may not keep up with changes in microbial resistance. Failure to follow guidelines has been documented, but the consequences are unclear. In a large primary care setting, of the 30% of patients with UTIs who would have met criteria for guideline directed therapy only 25% were treated in a manner compatible with the 1999 IDSA guideline [40]. A national, ongoing survey of prescribing practices shows that fluoroquinolone use is steadily increasing, in fact fluoroquinolones have now surpassed TMP/SMX as the preferred treatment for uncomplicated UTIs in ambulatory women [41]. While there are some regional differences, the overall trend appears to be an increase in the use of fluoroquinolones to treat older women. There

is debate about whether fluoroquinolones are appropriate first-line agents (especially with the reduced acquisition cost of generic ciprofloxacin) particularly given the potential problem of unnecessary use leading to increased resistance. A more nuanced approach of using TMP/SMX as first-line therapy for uncomplicated cystitis and having roles for nitrofurantoin and fosfomycin as fluoroquinolone sparing agents has been proposed but not formally tested in clinical trials [42].

Prognosis

While withholding therapy from an otherwise healthy ambulatory woman with dysuria and a positive urine culture would be difficult for most clinicians, there are some data on the expected outcome. A randomized trial in Belgium studied the benefit of a 3-day course of nitrofurantoin (100 mg orally every 6 hours) with a similar schedule of placebo [43]. Although 166 women were screened, only 78 had pyuria and agreed to participate. Thirty-five women in each group were evaluable at the conclusion of therapy and 77% of the nitrofurantoin recipients were better as compared with 54% of the placebo recipients. Excluding women with negative urine cultures showed that 17/23 (74%) of the nitrofurantoin recipients versus 9/22 (41%) of the placebo recipients were better at the 7-day evaluation. While this confirms a considerable benefit of antimicrobials for UTI (NNT for various favorable outcomes ranged from 1.7 to 4.4), clinical and microbial success was fairly common without any active treatment. In one metaanalysis of six double-blind clinical trials (over 3000 patients), the following four factors were associated with better outcomes [44]:

- not using a diaphragm
- treatment for $\geqslant$3 days
- symptoms for $<$2 days
- African-American race.

Patients infected with bacteria categorized as *Klebsiella* or "other" had a worse prognosis.

Response to treatment is usually fast although it may take days for all symptoms to resolve. There is even some clinical success in women with organisms that are reported to be resistant to the drug chosen for treatment. This might result from spontaneous cure or from achieving high enough a concentration of antimicrobial in the urine to result in cure despite apparent resistance. In an Israeli study [45], all patients received a 5-day course of TMP-SMX and, in the patients with strains that were susceptible, the success rate was 82% as compared with 42% in whom the organism was resistant. In a large British study showing a relatively low incidence of trimethoprim resistance (14%), half the patients with in vitro resistance to trimethoprim receiving a 3-day course of trimethoprim were symptomatically resolved in 1 week [46]. The time to resolution of symptoms was longer (when it occurred), but given the rate of resistance and the fairly good clinical response even in patients with resistant strains, the authors calculate that they would need to treat 23 patients to find one who returned for retreatment. Thus they make the case for continued empiric therapy with TMP/SMX without the need for a pretreatment urine culture. In areas where resistance is more frequent to usual first-line agents, the approach is to use a second-line agent such as fosfomycin or an alternative (but perhaps more expensive) first-line agent such as a fluoroquinolone. The same would be true for women who are allergic or cannot tolerate the usual medical interventions. Differences in resistance patterns can be associated with geographic location, patient age, and gender. A large multicenter study of antibiotic resistance in outpatients with UTI looking at nearly 2000 uropathogens collected in the US and Canada between 2003 and 2004 illustrates some of these differences [47]. The 175 patients under the age of 15 had almost no fluoroquinolone-resistant bacteria although they were more likely to have bacteria with ampicillin, nitrofurantoin, or TMP/SMX resistance than was found in adults. Younger adults (15–50) had less fluoroquinolone resistance than older adults ($>$50). Regional and gender differences likely reflect variations in circulating strains of potential uropathogens in the gastrointestinal tract as well as the selective pressure of antimicrobial use.

Pathogenesis

The sequence of events that follow the entry of uropathogens into the bladder is now better understood. The host innate immune process, using Toll-like receptors, begins a variety of nonspecific consequences including more rapid shedding of bladder mucosa to avoid infection [48]. The proper

physiologic functioning of Toll-like receptors seems to coordinate the inflammatory response. In an animal model, mice with defective Toll-like receptors could not marshal a neutrophil response to a kidney infection and did not develop the pathologic features of pyelonephritis [49]. A similar phenomenon can be shown in the bladders of animals with defective Toll-like receptors after local challenge with bacteria. However the uropathogen can hide within the cells of the bladder and create a large number of copies within a biofilm coat. This accounts for the difficulty for some people to clear the infection despite a paucity of initial symptoms. On the other side of the ledger, we know that bacteria in the process of causing infection upregulate a variety of virulence genes such as adhesins (e.g., type 1 fimbriae) and iron acquisition systems while downregulating motility and chemotaxis-related genes as a way to maintain colonization/infection once in the uroepithelium [50].

Case presentation 2

A 63-year-old woman is seen in the office for a 2-day history of dysuria. She had recently retired from her secretarial job because of complications of her diabetes (early cataracts and mild, painful neuropathy) that had made it difficult for her to travel to work. She had recently completed a course of cefadroxil for cellulitis of the left foot with clinical improvement. Her current voiding symptoms were moderately severe. She thought she might have had a fever and some mild sweats but at the time of the clinic visit she was afebrile. The remainder of the examination was unremarkable except for mild left costovertebral angle tenderness and diminished sensation in both feet. A pelvic examination was normal. A urine specimen was obtained: the dipstick test was positive for leukocyte esterase and glucose and negative for all other tests including nitrite.

Like the previous patient, this woman also has a short history of irritative voiding symptoms, but there are some important distinctions. In addition to being older, this patient has longstanding diabetes with complications. As a result, bladder dysfunction due to diabetic neuropathy is a possibility. This patient's previous course of antibiotics (cephalosporins) may have changed the specific potential uropathogens, and may specifically have selected a more antibiotic-resistant flora [51]. The presence of significant diabetic peripheral neuropathy might portend autonomic neuropathy and incomplete bladder emptying. Significant residual bladder urine increases the risk of upper tract infection and treatment failure as well as the intrinsic risk for cystitis [52,53]. There are two potential strategies with respect to obtaining urine cultures for this patient:

- obtain a culture before initiating antibiotics (early culture)
- obtain a culture only if there is a clinical failure of therapy (late culture).

Early culture is reasonable when urine can be obtained in the office and if culture reports are promptly and reliably available. On the other hand, a late culture strategy makes sense if cultures are difficult to obtain and if adherence with medication and follow-up is likely to be excellent. These strategies have not been formally compared in clinical trials.

Case presentation 2 (continued)

Because of the patient's recent antibiotic course, a urine culture was requested. While culture results were awaited, the patient began a course of antibiotics with TMP-SMX (160/800 mg orally twice a day) with the intention of giving a 14-day course of treatment. The laboratory report on the culture showed that she had an *E. coli* that was resistant to ampicillin and tetracycline but susceptible to all the other agents tested. The patient responded clinically within 2 days of starting treatment. At the conclusion of her 14-day course of therapy, she was asymptomatic and, at the time of follow-up clinic visit, had no symptoms or physical findings of UTI.

Follow-up

Follow-up for the woman with a symptomatic UTI is simple. If all symptoms have resolved, the treatment is considered successful and no further visit or diagnostic testing is needed. Both of the cases presented had good responses and would not need follow-up. It would be sufficient to have telephone contact to

assure that the treatment was successful. The success rate with TMP-SMX in the IDSA study [54] was 93%, and the majority of treatment failures were symptomatic. In a large primary care database (104 099 infections) in the UK, the failure rate (i.e., need for a second course of therapy) was 14% at 28 days of follow-up after the diagnosis of UTI was first made [51]. This study included women treated in 1992–99. Of all the drugs used, TMP-SMX was the least likely to fail with a hazard ratio (HR) for failure of 1.39 for amoxicillin and 1.23 for nitrofurantoin, although ciprofloxacin (HR for failure of 1.12; 95% CI 0.90–1.40) and cefadroxil (HR 1.17; 95% CI 0.93–1.48) were of comparable efficacy but were used much less often than TMP-SMX. There are certainly limitations of this nonrandomized study design, but the large number of women studied gives some indication of the likelihood of a successful outcome, even though treatment was assigned by physician preference and not controlled. Since this study did not look at the result of follow-up cultures, but only at the need for another course of antimicrobials, it is difficult to know whether to look for early failure with scheduled culture before the recurrence of symptoms. Since failure requiring retreatment is expected in about one in seven patients, and these failures can occur within a few days of the conclusion of the original therapy to a month later, the usefulness of routine follow-up cultures is questionable.

Asymptomatic bacteriuria

Asymptomatic bacteriuria refers to the presence of significant numbers of bacteria in the urine in the absence of symptoms such as urinary burning, frequency, or urgency. In young, healthy women, the prevalence of asymptomatic bacteriuria is 5–6% [55]. In this study, it was shown that, in the vast majority of cases of asymptomatic bacteriuria, the bacteriuria resolves spontaneously. However, the likelihood of developing cystitis within a week of the detection of asymptomatic bacteriuria is eight times higher than the risk within a week of having a sterile urine culture. Thus, in this setting, asymptomatic bacteriuria is an uncommon and unalarming entity that has a small chance of progressing to symptomatic disease. Underlying conditions known to be associated with higher rates of asymptomatic bacteriuria are pregnancy, post-bladder catheter removal, advanced age (>65 years), and diabetes mellitus. There is evidence favoring treatment of asymptomatic bacteriuria during pregnancy [56,57] and following bladder catheter removal [58]. A Cochrane review of bacteriuria in pregnancy showed substantial benefits of treatment for asymptomatic bacteriuria during pregnancy. The elimination of bacteriuria was much greater with antibiotics than with placebo or no treatment (OR 0.07; 95% CI 0.05–0.10), the reduction of pyelonephritis was impressive (OR 0.24; 95% CI 0.19–0.32), and the pregnancy outcome (fewer preterm or low birthweight babies) was enhanced (OR 0.60; 95% CI 0.45–0.80). A randomized controlled clinical trial demonstrated that bacteriuria resolved spontaneously within 14 days of bladder catheterization in 36% and after a single dose of antibiotics in 81% [58]. More importantly, of the women who received no treatment, seven of 42 developed symptomatic UTIs. In general, untreated women under the age of 65 did better at clearing their bacteriuria (74%) than older women (4%). Without controlled trials, this could be interpreted as a suggestion to promptly treat bacteriuria after catheter removal in older people but to wait for symptoms to emerge in younger ones. Post-procedure bacteriuria can occur after cystoscopy. Patients with known bacteriuria are often treated before invasive procedures (including surgery and cystoscopy). There is evidence that prophylaxis with a single dose of pre-procedure ciprofloxacin can appreciably reduce the risk of post-cystoscopy bacteriuria in women with negative urine cultures undergoing diagnostic cystoscopy [59]. In other settings such as diabetes and old age, attempted treatment of bacteriuria is unhelpful in preventing subsequent infections and exposes patients to the potential toxicity of antimicrobials and the cost of repeated clinic visits and urine tests [60,61]. A recent prospective, randomized trial of treatment of asymptomatic bacteriuria in diabetic women showed no net benefit for a 14-day course of antibiotics directed at the organism isolated [62]. There was no reduction in symptomatic UTI in a 3-year follow-up, but there was a considerable excess in the use of antibiotics (5-fold increase) and in treatment-related adverse effects (3-fold increase). A minor side note: a 3-day course of antibiotics for the eradication of asymptomatic bacteriuria was ineffective in all six cases in which it was tried, so that regimen was dropped from the study.

Case presentation 2 (continued)

Three months later, the patient noted the onset of dysuria and urinary frequency over a period of 2 days. At the time of the office visit, she was uncomfortable but had no fever or constitutional symptoms. Her urinalysis again showed a positive leukocyte esterase on the dipstick and a large number of white blood cells on microscopic analysis. She was given another course of TMP-SMX after a urine culture was sent. This time, the culture showed >100 000 colony-forming units of *Klebsiella pneumoniae.* This organism was resistant to ampicillin but susceptible to all other antibiotics tested.

In this situation, the patient had a new infection after cure of the previous UTI. Recurrence of UTI is a common problem with rates reported as high as 44% at one year [63]. Recurrent symptoms following apparent cure of a UTI can represent a relapse of the previous infection or a reinfection. In this case, the patient clearly had a reinfection since the organism isolated was a different species from that of the prior infection. To document a relapse, it is essential to demonstrate not only the same species of bacteria in both infections but also the same strain. This can be done using molecular typing.

Case presentation 2 (continued)

Although she felt completely well at the conclusion of her second course of antibiotics, the patient is frustrated and asks, "Why does this keep happening to me? Can't something be done to prevent another one of these infections?"

Prevention

Although the reservoir for organisms causing UTIs is the lower gastrointestinal tract, it is unclear exactly how uropathogens become part of our flora. A large multi-state study done among attendees of college health services showed that variants of an *E. coli* clone were circulating as uropathogens in at least three US states [64]. Women with UTIs were not acquainted with each other. Men from the same campuses were also colonized by these strains although there was no reported excess of UTIs among them. These clones had in common a resistance to TMP/SMX, but it is likely that more common strains are in national circulation causing epidemics of UTIs. In a follow-on study in the same general population, the clonal group found in all three geographic regions was still present but had decreased by 38% within 2 years of the original collection [65]. On a smaller scale, it has been shown that members of a household (including the family dog) can also be part of a gastrointestinal tract uropathogen-sharing network even if most of them have no UTI [66]. Individual susceptibility to pyelonephritis seems to be partially familial. In addition to variations in cellular adhesins that make genital and bladder colonization more common (e.g., secretor status and blood type O), it appears that expression of CXCR1 is lower in pyelonephritis patients and their relatives than in controls or people with cystitis but no upper tract involvement [67].

The timing and frequency of recurrent UTI is unpredictable. Most of the known risk factors for UTI are difficult to control. Efforts to reduce the adhesion of uropathogenic bacteria to the genitourinary epithelium by the ingestion of cranberry juice have been mildly effective while the use of a lactobacillus GG beverage was not helpful in preventing UTI [68]. Women who were at risk of recurrent UTIs were randomized to receive a cranberry/lingonberry juice daily or lactobacillus GG for 5 days/week. The study was not blinded, although the investigators were not informed which treatment the women were getting. In a 6-month period, the women using the cranberry beverage had a 20% absolute reduction in the rate of UTIs (95% CI 3–36). There was a very slight increase in the absolute rate of UTIs in the group taking the lactobacillus beverage. Cranberry juice prophylaxis was studied as a preventive measure for hospitalized, elderly patients although the 50% reduction in symptomatic UTIs was not statistically significant [69]. Cranberry juice prophylaxis for ambulatory women was studied in a Cochrane systematic review and found to be somewhat helpful for those who can tolerate it [70]. Change in vaginal pH, in particular the use of spermicide (often accompanying diaphragms), has been associated with an increased risk of UTI in

several studies [3,71]. Sexual activity can predispose to UTIs [3] and this may be especially problematic with newer sex partners. In postmenopausal women, not taking estrogen replacement therapy is a risk factor for recurrent UTI [52]. Topical or systemic estrogens will reduce the rate of recurrent UTI in these women [72]. Clearly, the use of systemic estrogens should be informed by their risk/benefit for medical problems other than UTI.

The controversy over seeking an anatomic explanation for recurrent UTI is not fully resolved, but in adults it is rare to identify correctable lesions [73]. In this study, 104 adult women referred to Urology for UTI consultation were evaluated with excretory urography and 74 of them also had cystoscopy. These women had a heterogeneous history of UTI, but most had had two or more UTIs in the past year. The radiographic work-up showed only 12 abnormalities of which perhaps five were related to (but not likely to be causal of) UTI. The cystoscopies showed that 18% of the women had abnormalities (most of which were mucosal inflammation) and that only 4% had a potentially treatable problem (urethral diverticula). For our patient, bladder function could be abnormal if she also has an autonomic neuropathy from diabetes. Obstructions to urine flow, poor emptying of the bladder and ureters, reflux of urine from the bladder to the ureter, and anatomic variations of the urethra can be found as causes of recurrent infection. However, standard techniques (radiographic imaging, cystoscopy, etc.) have a low yield in identifying such lesions [73]. Relatively common problems such as incomplete bladder emptying because of neural injury or disease are often difficult or impossible to correct.

Evidence exists to support antimicrobial prevention of recurrent infections. Women with frequent, uncomplicated recurrences (usually two or more infections in a 6-month period) may benefit from one of three antibiotic use strategies:

- continuous low-dose prophylaxis [74,75]
- postcoital prophylaxis [76]
- pre-emptive short course treatment (without medical consultation) at first sign of infection [77].

Each of these strategies reduces the frequency and morbidity of UTI, but there are no controlled trials comparing them. Postcoital prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) was studied in a randomized, placebo-controlled trial and shown to reduce UTIs by 12-fold (from 3.6 per patient year to 0.3 per patient year) [76]. However, the very small number of women studied (16 in the TMP-SMX group and 11 in the placebo group) limits its precision. Self-directed therapy appeals to many women, and there is evidence that women who have experienced UTI can self-diagnose and treat with impressive accuracy and good outcomes [78]. In this study, 172 women were given the opportunity to initiate levofloxacin therapy at the first indication of a UTI. There was no control group since all women were eligible to initiate therapy after obtaining a urine specimen for analysis and culture. Roughly 50% of the women studied had one or more UTIs after enrolling in the study (on average, two per woman for those who had UTI), and the urinalysis and/or urine culture was positive in 95% of these episodes. Clinical and microbiologic cures were attained in 92% and 96% of cases, respectively. Old trials of daily prophylaxis with TMP/SMX or fluoroquinolones showed benefits over placebo, but a newer placebo-controlled study of 317 women showed potential benefit of fosfomycin for women with at least three UTIs in the prior 12 months [79]. A single sachet of 3 g of fosfomycin was dissolved in water and taken orally every 10 days for 6 months and the infection rate of 0.14 infections per patient year was much lower than the 2.97 infections per patient year of placebo recipients ($P < 0.001$).

Whether prophylaxis is offered or not, there tends to be a slow trend towards cessation of recurrent infections in women without anatomic or physiologic reasons to have recurrent UTI. For women on continuing prophylaxis or postcoital prophylaxis, it might make sense to stop this treatment every year or so to see if the propensity to recurrent infections has faded. The patient in Case 2 will need to be aware of her urinary infection pattern and attend to her possible bladder dysfunction. This may entail consultation with a urologist who can assess her urodynamics and help determine the best way to maintain good voiding patterns.

The use of special silver-coated catheters in people who need short-term bladder catheterization has been studied and been shown to reduce the risk of UTI. A randomized crossover study in hospitalized patients showed that the relative risk of infection per

100 catheters used was 0.68 (95% CI 0.54–0.86) [80]. A report prepared for the US Agency for Healthcare Research and Quality indicated that silver-coated catheters could prevent bacteriuria and complications of UTI such as bacteremia, although these benefits might be somewhat vitiated with a long duration of catheterization [81]. This paper describes a number of randomized controlled trials of various silver-coated catheters versus standard silicon urinary catheters. The range of benefits is broad from a 4-fold reduction (at most) to no meaningful reduction. This large variation is related in part to differences in the patient populations and in the duration of catheterization. A systematic review of antimicrobial urinary catheters emphasized the lack of conclusive evidence that can be derived from 12 trials comparing nitrofurazone- or silver-coated catheters with standard ones [82]. The largest and newest studies showed the smallest effect on bacteriuria, and none of them showed an effect on clinically important outcomes such as hospital stay, antibiotic administration, or other morbidity. On the other hand, a careful bladder management plan in the perioperative setting was shown to have a substantial reduction in bacteriuria among orthopedic patients [83]. Even 2 years after the formal intervention period the 60% reduction in bacteriuria persisted, which suggests that an easy-to-implement protocol can have lasting benefits.

The problem of UTI in people with spinal cord injury has also led to the study of preventive measures. The US Agency for Health Care Policy initiated a metaanalysis of the role of prophylactic antibiotics in adults and adolescents with neurogenic bladder secondary to spinal cord injury [84]. They showed a reduction in the number of episodes of asymptomatic bacteriuria but not in the number of symptomatic UTIs. This calls into question the practice of aggressive prophylaxis, especially in an environment of rising rates of *Clostridium difficile* colitis. Patients with spinal cord injuries are also a target population for a new concept in infection prevention: bacterial interference. *E. coli* strain 83972 isolated from a child with persistent, symptom-free bacteriuria has been shown to reduce both bacteriuria and UTI in a placebo-controlled trial where it was instilled into the bladder and established colonization [85]. Other trials are under way, and this may be an attractive option in other patient groups with a risk for recurrent UTI [86].

Urinary tract infections in men

Case presentation 3

A 40-year-old man presented to his physician with a 3-day history of dysuria. The pain was moderately severe but only present during voiding. He had no urethral discharge and he had no pelvic pain. He had not been sexually active for over 1 month prior to his dysuria. On examination, his temperature was 37.4°C and the general physical examination was normal. The rectal examination showed a mildly enlarged but nontender prostate. Urine analysis showed pyuria and bacteriuria. Urine culture was obtained and he was given ciprofloxacin 750 mg every 12 hours pending culture results. The culture eventually showed 10^5 colony forming units per mL of *Escherichia coli* susceptible to ciprofloxacin.

Clinical presentation

The presentation in this case is comparable to UTIs that are seen in women. However, in men it is important to consider involvement of the prostate gland as well as the bladder, ureters, and kidneys. The literature on UTI in men is limited and groups together urinary infections, such as cystitis and pyelonephritis, with prostatitis. It is easy to "rule in" prostatitis with a variety of clinical features (prostate tenderness, post-prostate examination urethral discharge) because acute prostatitis is often defined as a UTI in a man with additional features supporting prostate inflammation [87]. However, in men with features of UTI, it can be impossible to rule out some degree of prostatitis at the time of initial diagnosis since there may be only subtle or subclinical features of prostate involvement, which would only be revealed by prostate biopsy or culture of prostatic secretions. Thus the absence of prostate tenderness or post-prostate examination urethral discharge does not exclude the possibility of prostatitis in a man with dysuria and positive urine cultures [87]. Because of this overlap, acute prostatitis and UTI can be considered to form a continuum in men. Some older literature refers to this as "recurrent UTI in men" or chronic prostatitis because of the incomplete response to the short courses of antibiotics used at the time [88].

Prostatitis

Prostatitis is a common condition and has protean manifestations. Several classification schemes have been devised to account for the variable characteristics that can be present. An NIH consensus classification has been developed to standardize prostatitis variants and permit more meaningful research [89]. This system creates four categories:

- acute bacterial prostatitis
- chronic bacterial prostatitis
- chronic prostatitis/pelvic pain syndrome (with inflammatory and noninflammatory subtypes)
- asymptomatic inflammatory prostatitis.

Although having reproducible definitions for the advancement of clinical research is reasonable, this division is difficult to translate into everyday clinical practice. Acute and chronic bacterial prostatitis share similarities with UTI since all three are infections. However, it is much less clear what the relationship is between infection and the other two forms of prostate disease. The exact distinction between acute and chronic bacterial prostatitis in this working definition is imprecise and does not specify the number of days of symptoms needed to invoke a diagnosis of prostatitis. This difficulty is also reflected in clinical trials of bacterial prostatitis. Of interest, it is widely believed that the chronic bacterial and nonbacterial forms of prostatitis account for about 90% of cases of prostatitis. A large population-based study in Canada showed that nearly 10% of men (aged 20–74) had symptoms consistent with prostatitis other than acute bacterial prostatitis and there was a fairly smooth age distribution throughout the group [90]. A similar survey in Minnesota also showed that 9% of men (aged 40–70) had symptoms typical of prostatitis other than acute bacterial prostatitis [91]. However, among men with prior prostatitis (including acute bacterial prostatitis), there was a significant increase in the age-related risk of prostatitis (20% at age 40, 38% at age 60, and 50% at age 50), suggesting that the various chronic prostatitis syndromes can have a remitting/relapsing form that tends not to resolve completely irrespective of the intervention.

Diagnosis

The diagnosis of UTI in men is made in a similar fashion to that in women. Urine collection is less likely to be compromised by contamination from skin flora. Pyuria and bacteriuria are both highly predictive of significant positive cultures. The lower limit of a positive quantitative culture is 10^3 colony-forming units per mL [92]. The sensitivity and specificity of this cut-off were both 97%, and it was unimportant as to whether a clean-catch mid-stream specimen or an uncleansed first void specimen was used.

Other investigations

The evaluation of the cause of UTI in men differs from that in women since it is believed that there should be some diagnosable anatomic or physiologic factor to account for the UTI in men [93]. Recent studies in this area mostly come from referral centers and thus may suffer from referral bias. For example, a Scandinavian study of 83 men with UTI showed that 19 men had some upper tract finding and 35 men had lower tract problems [94]. There was a correctable defect in only one man with an upper tract lesion, but 41% of the men had a lower tract abnormality. Only 18% of the men were found to have previously unrecognized, correctable abnormalities with the multiple modalities used to study the lower tract: cystourethroscopy, uroflowmetry, digital rectal examination, and measurement of postvoid residual by abdominal ultrasound. There is no mention of how many of these men actually underwent a corrective procedure. A study designed to compare intravenous urography (IVU) with ultrasound and plain film showed that half of the men studied had some abnormality (most of which were not correctable) [95]. The most common problem found was bladder outflow obstruction that was actually diagnosed by urodynamics (which was not part of the formal study protocol but was available for many but not all of the patients). There was no mention of how many men received treatment for any abnormality found. A community-based study from Australia showed that of gay men with UTI (one-third of whom were HIV positive), clinical management was satisfactory and, of the men who underwent further investigation, only 14% had detectable abnormalities [96]. Again there was no report on how many of these men underwent a corrective procedure. One thing lacking in all these studies is a sense of the rate of baseline abnormalities in similar populations of men without UTIs. Given the high rate of prostate symptoms recorded in community-based surveys [90,91], UTIs might simply

coexist with some of the voiding problems and other prostate complaints seen in so many men. An additional issue that might be contributory is the referral bias of the studies performed by urologists [94,95]. If the primary care providers suspected some anatomic or physiologic problem in these men, they might have referred them for evaluation more quickly than for men with UTIs who evinced no symptoms.

Treatment strategies for men

The organisms that cause urinary tract infections in men (including acute and chronic prostatitis) are essentially the same as those found in women although the relative rates will vary [14]]. The same virulence factors (P fimbriae, adhesins, hemolysins) that make bacteria good uropathogens in women (particularly as a cause of pyelonephritis) also make them uropathogenic in men [97–99]. Thus, *E. coli*, *Klebsiella* spp., *Enterococcus* spp., *Proteus* spp., and various other gram-negative bacteria comprise the vast majority of uropathogens in men.

There are few studies comparing treatment strategies for male urinary tract infection or prostatitis in randomized controlled trials. There are no systematic reviews. Because of the possibility of concurrent prostatitis in men with UTI, the drugs selected for initial therapy are often those that penetrate into the prostate gland. These include TMP and the fluoroquinolones. Whilst other classes of drugs may be effective in the treatment of UTI in men, these drugs are active against most uropathogens. TMP is often given in a fixed combination with SMX. Clinical trials of TMP-SMX for UTI in males have, however, been disappointing. In an effort to compare a short course (10 days) to a long course (12 weeks) for recurrent UTI, the investigators of a multicenter US Veterans Administration study tried to recruit appropriate patients to randomize [100]. Of the 306 patients screened, only 38 were randomized and only 30 were available for analysis at the end of the study period. Of the men screened, 17% were excluded because of comorbidity, 28% for paramorbidity, 6% for comedication, 24% for lack of compliance, and 9% for miscellaneous reasons. This left 46 men to study. Four of them did not have meaningful outcome on localization tests (which would likely not be considered very important today, but were required for study entry). Of the 42 remaining men, four could not be randomized. Eight more were dropped from the study for a variety of protocol violations, leaving a total of 30. Notably, fewer than half of the men studied were symptomatic from their UTI, and two did not even have pyuria. Of interest, the long course of therapy was superior – 60% success for 12 weeks and only 20% for 10 days (RR 3; 95% CI 1.01–8.95). Recurrent infections were from the same organism in the majority of cases. Another study of 42 men with recurrent UTI showed that a longer course of treatment (6 weeks vs 2 weeks) had a lower failure rate at a 6-week post-treatment follow-up visit (68% vs 32%; RR 2·2; 95% CI 1.05–4.49) [101].

In contrast to TMP-SMX, the clinical response to fluoroquinolones in men with UTI is much better. Fluoroquinolones have good prostate penetration in animal models, and agents studied appear comparable in the treatment of male UTI/prostatitis. When norfloxacin was compared with TMP-SMX in 109 men in a randomized controlled trial, the bacterial eradication rate of 93% with norfloxacin compared with 67% with TMP-SMX ($P < 0.05$) [102].

Ofloxacin, a drug that has largely been replaced by its L-isomer, levofloxacin, was studied in an unblinded comparison to indanyl carbenicillin (an oral form of the drug that has an FDA indication for UTI/prostatitis) and to TMP-SMX [103]. The population included men and women in equal numbers; however, treatment arms were not stratified by gender, an important limitation. Treatment failure with carbenicillin was 25% compared with no treatment failures with ofloxacin (0%) ($P = 0.048$). The comparison with TMP-SMX was done in a larger group (173 patients) and the outcomes were similar in both treatment arms, although the trend for clinical cure favored ofloxacin. Only 117 patients were evaluable for clinical cure: 93% of ofloxacin-treated patients were cured as compared with 85% of TMP-SMX-treated patients for an RR of 0.92 (95% CI 0.81–1.04).

In another study, ciprofloxacin was compared with TMP-SMX in men with UTI [104]. There was no significant difference in outcomes at late follow-up (4–6 weeks), but the early bacterial eradication rate (days 5–9 following antibiotics) favored ciprofloxacin (82% vs 52%, $P = 0.035$). The drug doses used in the study were low (ciprofloxacin 250 mg orally every 12 hours, and TMP-SMX 160/800 mg orally every 12 hours) and the duration was brief (mean of 7 days).

An open-label study of ciprofloxacin for chronic bacterial prostatitis showed a good outcome with a 4-week course [105]. The bacteriologic cure rate was 92% at 3 months after the end of therapy and 70% at 2 years post therapy. A randomized trial comparing 2 vs 4 weeks of ciprofloxacin for men with febrile UTIs showed no significant difference in either early response or at 1-year follow-up [106].

How does this evidence apply to the example of the patient in Case 3 above? The treatment with ciprofloxacin is rational and should be of at least 2 weeks' duration. Assuming that he makes a good recovery and has no further symptoms, he does not need investigative studies, but incomplete resolution or relapse should occasion a work-up. An ultrasound and plain abdominal radiograph can look for structural lesions such as kidney stones or hydronephrosis. A urologic evaluation could find problems with bladder emptying or structural disease of the lower urinary tract (including the prostate gland). While his prognosis is good, he may require a longer course of antibiotics for subsequent UTI. Treatment benefit is less optimistic for men with chronic prostatitis/chronic pelvic pain syndrome. A multicenter 6-week trial of levofloxacin vs placebo in 80 men showed some improvement in both groups but no benefit of the antibiotic over the placebo [107]. A double-blind, randomized trial of nearly 200 men compared ciprofloxacin plus tamsulosin, ciprofloxacin plus placebo, tamsulosin plus placebo, and two placebos [108]. The four groups were indistinguishable in terms of clinical response or measurement of disease using the NIH scoring system.

Severe and complex urinary tract infections

Case presentation 4

A 59-year-old diabetic woman with no other prior medical problems was seen in the Emergency Department with a 36-hour history of fever, chills, and flank pain. She attempted to go to work that day, but after 2 hours at the office, her co-workers became alarmed when she nearly fainted on the way to the copier. In the ED, she was slightly confused and sweaty. Her oral temperature was 38.9°C, pulse 110, and respiratory rate 24. Her blood pressure was 92/60 mmHg. She had right flank tenderness on palpation. Urine obtained by bladder catheterization was cloudy and had numerous WBC and bacteria on microscopic examination. She had a WBC of 22 000 with 80% PMNs, 14% bands, and 6% lymphocytes. Her fingerstick blood glucose was 21 mmol/L and her creatinine was 100 μmol/L.

This patient has a severe urinary tract infection requiring hospital admission [5]. In addition to fever and flank tenderness, she has signs of possible sepsis with hypotension, rapid heart and respiratory rates, and mental clouding. Furthermore, her diabetes is out of control and she is dehydrated. Based on her clinical presentation, she has upper urinary tract disease (kidney, renal pelvis, or ureter), otherwise known as pyelonephritis.

Because this woman is diabetic, she could be presenting with a complicated UTI. This is defined as either a disruption of the normal anatomy or physiology (as in this patient) of the urinary tract. Obstructions to urine flow such as stones, tumors, or strictures can lead to more clinically severe infections. Alterations to barriers that normally maintain the unidirectional flow of urine such as vesicoureteral reflux and external bladder catheters can also predispose to severe infections. The presence of stones or catheters can also contribute a surface for the growth of microbes as well as some protection from host defenses such as complement and phagocytosis. Physiologic problems such as incomplete bladder emptying with residual urine or poor ureteral muscular function can contribute to UTI complexity. Risk factors for pyelonephritis are similar to those of cystitis: sexual activity, family history, diabetes, and incontinence [109].

Diagnosis of severe urinary tract infections

The diagnosis of severe UTI starts with urine collection for urinalysis and culture. Quantitation of pyuria or bacteriuria cannot distinguish mild from severe UTI. A review of quantitative pyuria in 1983 showed a sensitivity of 97% and a specificity of 98% for the finding of concomitant bacteriuria [110]. Pyuria and UTI in the setting of an indwelling bladder catheter is

still a topic of interest, but a recent study has shown that the high specificity of pyuria for bacteriuria (90%) is offset by a low sensitivity (37%) [111]. In a British hospital study, urine dipstick testing on hospitalized patients was highly sensitive (98.3%) for bacteriuria; negative results on leukocyte esterase, nitrite, blood, and protein had a 98.3% NPV [112].

Blood cultures are commonly performed in patients with severe UTI. The rate of blood culture positivity varies, but is rarely in excess of 20–25%, even in the most severe hospitalized cases [113]. In almost all cases, positive blood cultures have the same organism that is found in the urine and thus may add little to the determination of the specific etiology of the UTI [114]. Whether positive blood cultures are systematically associated with worse outcomes, such as prolonged hospitalization, has not been determined [115]. There is some evidence from a retrospective chart review that young women with severe UTI and positive blood cultures do have higher rates of genitourinary abnormality, persistent fever, and abnormal heart rate than women without bacteremia [116]. A study of pregnant women with severe UTI showed that those who were bacteremic had a longer hospital stay than those who were not [117]. The management implications for patients with positive blood cultures is hard to assess since they often have other markers of severity that call for more intensive treatment [118]. Positive blood cultures rarely surprise the clinician or independently change the therapeutic approach [119].

Site of care

The initial management of severe UTI includes a decision about hospitalization, which is based generally on the need for intravenous fluids, pressors, close nursing care, and adherence to a medical regimen. The patient in Case 4 might be stabilized in the Emergency Department, but would likely require hospital admission for assessment and treatment of her hemodynamic instability.

For patients with uncomplicated severe UTI, the choice of hospital admission greatly increases the cost of treatment. It is difficult to ascertain whether it improves outcome, however. This topic has not been studied in a controlled fashion except to show that for patients who can be managed in the ambulatory environment with oral therapy, there is no advantage to parenteral medications [120,121]. A retrospective survey of women evaluated in an Emergency Department showed that patients who were admitted (28 out of a total of 111) were older, had higher degrees of fever, were more likely to be diabetic or to have some genitourinary abnormality, or to be vomiting than women who were managed as outpatients [122]. The presence of vomiting was highly associated with admission (OR 12). It is notable that 12% of the patients initially discharged from the Emergency Department returned. A large population-based study of pyelonephritis in the Seattle area showed that the majority were managed in the ambulatory environment [4]. However the outpatient site of care was much more commonly chosen for women between 15–54 as compared to children, older women, or men of any age.

Treatment

After obtaining cultures and other laboratory tests, antibiotics are given empirically until susceptibility results are available.

The bacterial species that cause serious UTI are similar to those that cause cystitis. There is a preponderance of *E. coli* and other gram-negative rods. There are different phylogenetic characteristics and excess virulence factors in uropathogens causing pyelonephritis as compared to those causing cystitis or just found in normal fecal flora [123]. These bacteria usually have the same adherence properties as the ones that cause lower tract infection but may have additional virulence attributes that permit ascent of the ureter and in some cases deeper invasion such as bacteremia. The implication is that only a subset of cystitis strains are destined to cause pyelonephritis and this subset is not commonly present in the normal fecal flora. For the very ill patient in whom even a short delay in treatment could be significant, broad therapy is appropriate until culture results permit a narrowing. In many cases, fluoroquinolones will still be effective for treatment of UTIs, but prior exposure to fluoroquinolones is the most significant risk factor for the presence of a drug-resistant flora. This is true for resistance in gram-positive [124] as well as gram-negative [125] bacteria and irrespective of the indication for the previous course of fluoroquinolones. Many clinicians start with combination therapy to address the changing resistance patterns in patients with severe pyelonephritis – usually

the combination include two of the following three classes: broad-spectrum β-lactam, fluoroquinolone and aminoglycoside.

So long as there is no contraindication such as vomiting or hypotension, oral antibiotics are effective. In one study, route of administration of ciprofloxacin was randomized to intravenous or oral therapy with about 70 patients per arm [120]. Over one-third of the patients were bacteremic. There was no discernable difference in any of the outcome measures between oral and intravenous therapy, although the study was not powered to show modest superiority of either regimen. Because of the excellent bioavailability of oral ciprofloxacin, this outcome was not surprising. The presence of enterococci required a change in regimen in both groups, although the patients were doing well clinically at the time of the change. Among specific fluoroquinolones, there is no clear evidence as to which is most effective. This is largely because the comparative clinical trials have been powered for equivalence. For example, gatifloxacin was shown to be as effective as ciprofloxacin in a randomized trial evaluating 372 adults with complicated UTI and/or pyelonephritis [126]. In a smaller study, levofloxacin and lomefloxacin (the latter is no longer available in the USA) were comparable to ciprofloxacin [127]. Both of these studies used oral therapy.

There is evidence to suggest that for severe UTI, fluoroquinolones are superior to TMP-SMX. A randomized controlled trial comparing a 7-day course of ciprofloxacin with a 14-day course of TMP-SMX showed a better microbiologic and clinical outcome for ciprofloxacin at early (4–11 days) and late (22–48 days) follow-up [128]. The magnitude of the difference was roughly that for every 9–10 patients treated with ciprofloxacin there would be one less failure than if they were treated with TMP-SMX (NNT about 9–10). This was likely due to a fairly high rate of TMP-SMX resistance in the bacterial strains collected in this multicenter (25 centers) US study. While >90% of bacteria were *E. coli* as would be expected, 16% of the patients in the TMP-SMX arm had *E. coli* that were TMP-SMX-resistant. About half of these patients failed therapy (clinically and microbiologically) at the time of early follow-up. Although TMP-SMX is a very inexpensive drug, the pharmaco-economic analysis showed that the cost of treatment failures (such as repeat courses of therapy and repeat laboratory tests) made the TMP-SMX arm more expensive than the ciprofloxacin arm. A similar study today might show a different outcome depending on the relative frequency of isolation of bacteria resistant to these classes of antibiotics.

Aminoglycosides are another therapeutic option for severe UTIs. Almost all uropathogens from ambulatory patients are still susceptible to aminoglycosides (with the exception of *Enterococcus* spp.). However, careful monitoring is required because of the possibility for nephrotoxicity and ototoxicity. Modern once-a-day dosing schedules for aminoglycosides can reduce the risk of nephrotoxicity of a 7-day treatment course without sacrificing efficacy [129].

Other classes of drugs have been studied in equivalence trials for the treatment of severe UTI. In one study, piperacillin/tazobactam and imipenem were equivalent for severe UTI with a microbiologic success rate of about 50% for each [130]. In another study, patients were randomized to a single dose of intravenous ceftriaxone followed by oral cefixime versus daily intravenous ceftriaxone. Both groups of patients received a 10-day course of therapy and their outcomes were nearly identical. This cohort of patients was well enough to tolerate oral therapy after the first day and had a good outcome overall (about 75% bacteriologic and 90% clinical cure for each arm). Our patient in Case 4 might well be able to be discharged home after one or just a few doses of parenteral antibiotics.

Durability of response is a concern with severe UTI. In a comparison of hospitalized patients with severe UTI who received a short course of intravenous cefuroxime (for 2–3 days), patients who had follow-up with norfloxacin (a fluoroquinolone) did better microbiologically than those who had ceftibuten (a cephalosporin) [131]. The relative probability of bacterial eradication at 7–14-day follow up after the conclusion of therapy was 0.84 (95% CI 0.74–0.97) with ceftibuten being less effective. This seems to parallel the experience of β-lactams and fluoroquinolones for simple cystitis. This study did not explain why the responses were shorter lived for the cephalosporin, but it would be logical to assume that failure to eradicate the organism in other gastrointestinal and genital sites might have led to recurrence despite the 10-day course of therapy and the initial use of a parenteral cephalosporin. In some patients, duration alone may account for differences in outcomes. Patients with spinal cord injuries are prone to developing UTIs but there may be difficulty in correlating

clinical response with microbial response since the bacteriuria associated with relapse can be variably symptomatic. Nevertheless, a randomized trial comparing 3 vs 14 days of ciprofloxacin therapy for adults with symptomatic UTI in the presence of spinal cord injury showed a much higher rate of relapse in those who got the shorter course (RR 2.5 for early relapse and 2.1 for late relapse) [132].

As is the case with less severe UTIs, the prospect of more resistance can influence choices of initial therapy and may limit alternatives in the face of drug allergy. There is clearly an increase in resistance to TMP-SMX in the USA. Between 1992 and 1996 there was a doubling in the prevalence of TMP-SMX resistance in the Seattle area [133]. In the international arena, there is considerable variability of resistance – even within the USA, the range of resistance varies by region of the country [34]. In a review of resistance rates in the 1990s outside the USA, percentage of *E. coli* isolates resistant to TMP-SMX varied from 12% in Holland to 60% in Bangladesh, and resistance to fluoroquinolones varied from 0% to 13% in Spain and 18% in Bangladesh [134]. Bacteria with resistance patterns typical of hospital-acquired strains now threaten women with community-acquired UTIs. In addition to fluoroquinolone resistance, some community-acquired strains show extended-spectrum β-lactamase (ESBL) resistance to cephalosporins. In a Spanish study, there was a 3-fold increase between 2000 and 2003 in the isolation of ESBL-producing *E. coli* among ambulatory women with UTIs [135]. The strains were from several different clones but shared a CTX-M ESBL gene, suggesting that carrying this gene does not interfere with colonization of the healthy gastrointestinal and genital tracts. The only antibiotic exposure risk factor in this case–control study was exposure to a second-generation cephalosporin, cefuroxime (OR = 21), not third-generation cephalosporins or fluoroquinolones. In this study and others, the presence of ESBL genes was strongly associated with other resistance markers including those for fluoroquinolones and trimethoprim.

How quickly should a severe UTI respond to therapy?

This leads to a reasonable question of how quickly a woman with severe UTI should respond to therapy. Considering fever duration as an easily measured indicator of response, the answer is that there is a wide range of rates of improvement. A large retrospective survey of patients admitted with fever and UTI showed that the mean duration of fever ($T > 37.5^{o}C$ at some point during a 12-hour interval) was 39 hours with a median of 34 hours [136]. At 48 hours, about a quarter of the patients were still febrile. Elements associated with longer fever were increased serum creatinine, younger age, higher initial white blood cell counts, and the presence of *E. coli* as the causative agent. The interpretation of this data is difficult since the choice of hospital admission and initial antibiotics were completely uncontrolled. At the least it demonstrates that it is possible to see persistent temperature elevations in people who do well on therapy and have no underlying problems that predispose them to severe UTI. In fact the presence of persistent fever in a patient making a good clinical response is a poor reason to initiate a more detailed work-up for potentially complicated UTI, since fever was weakly correlated with abnormal results of imaging studies of the urinary tract that were done at the physician's request in some patients in this study.

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CHAPTER 10
Sexually transmitted infections

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Case presentation

A 17-year-old girl presents to the city sexual health clinic with vaginal discharge. She has a new boyfriend and is "on the pill"; she and her partner do not use condoms as their relationship "is monogamous." On examination, she has mild lower abdominal tenderness to palpation, cervicitis, and cervical discharge. There is cervical motion tenderness and left adnexal tenderness on bimanual examination. Her 17-year-old boyfriend has accompanied her to the clinic and is assessed separately; he reports a small amount of urethral discharge and mild dysuria. Examination reveals copious urethral discharge with meatal edema. A Gram stain of discharge reveals gram-negative intracellular diplococci. You review the literature to determine the following.

- How accurate is the clinical diagnosis of sexually transmitted infections (STI)?
- Do laboratory test results change the range of diagnostic possibilities in an individual with a possible STI?
- How helpful are historical and clinical findings in the diagnosis of pelvic inflammatory disease?
- Do condoms reduce the likelihood of transmission of STI?

STI are caused by a large and heterogeneous group of pathogens. Many of these pathogens can be transmitted by nonsexual as well as sexual routes; for example, enteric pathogens can be transmitted through food and water as well as via sexual intercourse. This chapter will focus on those infectious agents that are principally or exclusively transmitted via sexual contact, although the general principles described below can be applied to the larger group of STI. This chapter will not focus on human immunodeficiency virus (HIV) infection, which is discussed in Chapter 11.

STI are distinguished from other infectious diseases by several clinical and epidemiologic features. Perhaps most notable is the extremely high incidence of these infections; not withstanding likely underdiagnosis, *Chlamydia trachomatis* infection is the most common reportable infectious disease in the USA and Canada [1,2]. Herpes simplex virus type 2 (HSV-2) infection and human papillomavirus (HPV) infections are also extremely common: approximately 22% of adults in the USA have serologic evidence of HSV-2 infection [3]. Transient HPV infection is acquired through sexual activity by 33–55% of young adults in the USA and Europe [4–6]. Worldwide, it is estimated that over 330 million cases of syphilis, gonorrhea, trichomoniasis, and genital chlamydia infection occur annually [7]. The high incidence and prevalence of infection results in a high burden of disease, as well as large economic costs [8–11].

The burden of disease associated with these infections is further augmented by the synergistic relationship between non-HIV STI and HIV infection, owing to physical disruption of host mucosa, recruitment of immunologically active cells to the genital tract, and increases in HIV viral burden in genital secretions. A metaanalysis of observational studies generated a summary estimate of the relative risk of HIV acquisition in the context of another sexually transmitted infection to be 3.7 (95% CI 2.7–5.0%) (Fig. 10.1) [12].

However, STI other than HIV infection may also result in chronic medical illness or long-term complications. Genital chlamydia infection is associated with tubal infertility [13], ectopic pregnancies [14,15], and

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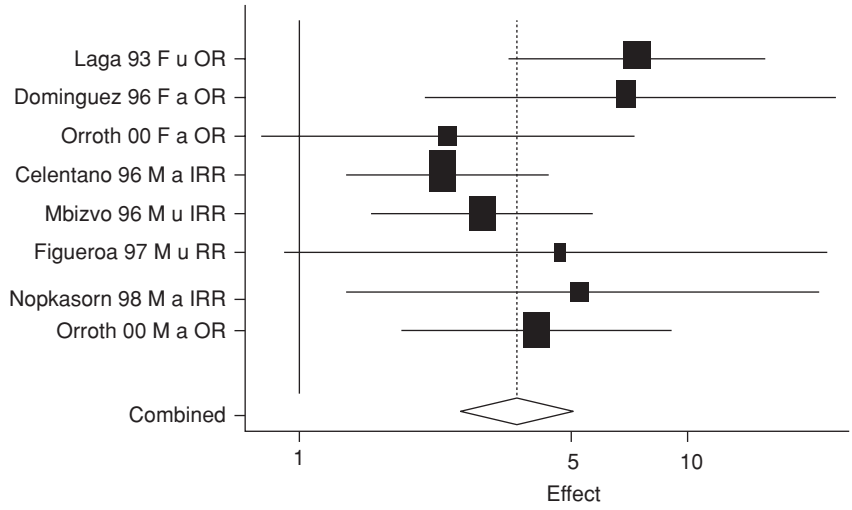


Figure 10.1 The impact of other sexually transmitted infections (STI) on risk of acquiring human immunodeficiency virus (HIV) infection. Forest plot showing the effect of other STI on HIV risk in individuals initially uninfected with HIV. Studies are listed on the vertical axis, with labels connoting author, year of publication, gender of initially uninfected partner, adjustment (a) or lack of adjustment (u) of effect estimate for other variables, and effect measure (OR, odds ratio; IRR, incidence rate ratio; RR, relative risk). Estimate of effect is plotted on the horizontal axis. The size of black boxes is proportional to study statistical precision, and horizontal lines represent 95% confidence intervals. The diamond represents the summary estimate of effect of sexually transmitted infection on HIV acquisition, and 95% confidence interval. Modified from reference [12]: Rottingen J, Cameron D, Garnett G. A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV. Sex Transm Dis 2001;28(10):579–97 with permission of Lippincott Williams & Wilkins.

chronic pelvic pain [16,17]. HPVs are strongly associated with cervical and anal cancers [18,19]. Infection of pregnant individuals with sexually transmitted pathogens may increase the risk of premature delivery, and may cause severe illness in the newborn [20–25]. This chapter will review the evidence for the clinical and microbiologic diagnosis of these infections, including evidence related to syndromic management (i.e., the use of more broadly targeted therapy in response to a clinical constellation of symptoms or signs). Evidence related to the interaction between contraceptive choice and STI is also reviewed. The second part of the chapter focuses on empiric and targeted management of STI, including some issues related to management in pregnancy. Finally, evidence of effectiveness for population-based STI prevention strategies is discussed.

Diagnosis of STI

Clinical and syndromic diagnosis

Sexually transmitted pathogens cause several common syndromes. Infection with *Neisseria gonorrhoea* or *Chlamydia trachomatis* frequently results in urethritis, cervicitis, or the constellation of symptoms and signs that suggest the presence of pelvic inflammatory disease. HSV, *Treponema pallidum*, and *Haemophilus ducreyi* are common agents of ulcerative genital disease, while vaginal discharge is commonly caused by infection with *Trichomonas vaginalis* or *Candida* species or by bacterial vaginosis.

The ability of clinicians to accurately diagnose infections caused by specific pathogens without the use of diagnostic tests appears poor. For example, a study involving a cohort of 446 men presenting to a New Orleans clinic found the clinical diagnosis of the causative agents of genital ulcer disease to be highly sensitive (94–98%), but nonspecific (31–35%) when compared with culture, microscopy, and serologic diagnosis (Table 10.1) [26]. Studies comparing clinical diagnosis of genital ulcer disease with the use of multiplex PCR have found similar limitations in clinician diagnostic accuracy [27–29].

The accuracy of bedside diagnosis of vaginitis based on clinical features and simple bedside tests

Table 10.1 Sensitivity and specificity of ulcer appearance in identifying specific etiologic agents of genital ulcer disease (modified from reference [26] with permission of the publisher)

Pathogen	Ulcer feature	Sensitivity (%)	Specificity (%)
Herpes simplex virus			
	3 or more lesions	63	64
	Shallow ulcer	60	88
	Moderate tenderness on examination	60	50
	All of the above features present	35	94
Hemophilus ducreyi			
	Undermined lesion border	85	68
	Moderate or severe tenderness on examination	57	52
	Purulent ulcer	64	75
	All of the above features present	34	94
Treponema pallidum			
	Indurated ulcer	47	95
	Nonpurulent ulcer	82	53
	Ulcer painless or minimally painful	67	58
	All of the above features present	31	98

(e.g., pH testing, whiff test, microscopic evaluation of "wet preps") also appears limited when compared with more comprehensive laboratory-based evaluations [30]. In a study performed in 153 women presenting to a clinic in Israel with vaginal discharge, only the finding of vaginal pH <4.5 was associated with infection by a particular pathogen (yeast); the positive predictive value of low vaginal pH for vaginal candidiasis was 68%.

Nonetheless, the limited availability of laboratory diagnostics in areas where STI are prevalent, combined with concern that patients will not return for treatment, has resulted in the development of the "syndromic" approach to diagnosis and treatment. In this approach, the presence of a given clinical history or constellation of physical examination findings results in the provision of broad-spectrum therapy targeting multiple treatable organisms [31,32].

Relatively simple diagnostic algorithms exist for such syndromes as genital ulceration, lower abdominal discomfort, and genital discharge. The term "sensitivity" as applied to these algorithms indicates the proportion of individuals with infections diagnosed by laboratory methods who receive appropriate therapy as a result of algorithm use.

A review published in 2000 evaluated studies of syndromic diagnosis and management of STI; this review included no controlled trials comparing diagnostic approaches [33]. Rather, attempts were made to validate algorithms using more comprehensive laboratory testing as a gold standard. Algorithms used alone have been associated with high sensitivity for urethral discharge (91–97%), genital ulcer diseases from syphilis or chancroid (68–100%), and vaginal discharge syndromes. However, diagnostic sensitivity is achieved at a cost of low specificity (as low as 7% in diagnosis of urethral discharge) and low positive predictive values. Thus the decision to use algorithms in settings where diagnostic tests are unavailable needs to be based on the prevalence and health impact of a given infection in the local population, and balanced against the potential consequences and costs of unnecessary antibiotic treatment.

Basic laboratory testing for urethritis and cervicitis

Nonspecific laboratory tests for the presence of gonorrheal and chlamydial cervicitis and urethritis include assessment of cervical, urethral, and vaginal white blood cell counts, urine leukocyte esterase testing, and the use of Gram stains. Most of these modalities have proven disappointing. For example, a study evaluating the use of cervical or vaginal white blood cell counts for the identification of gonorrheal

Table 10.2 Use of urine leukocyte esterase for the diagnosis of gonorrhea or chlamydia in men

Population or specimen source	Prevalence	Study gold standard	Sensitivity (%)	Specificity (%)	Reference
55 male STD clinic patients, Mwanza Region, Tanzania	Gonorrhea: 40% Chlamydia: 7%	Gonorrhea detected by culture, chlamydia by EIA	96	38	[370]
1095 ambulatory emergency room patients, Atlanta, Georgia	Gonorrhea: 2.5% Chlamydia: 3.9%	Gonorrhea and chlamydia detected by culture	41	90	[371]
479 male college students, Songkla Province, Thailand	Gonorrhea: 0.2% Chlamydia: 4.0%	Gonorrhea and chlamydia detected by PCR	26	11	[40]

or chlamydial cervicitis found no white blood cell cut-off to be both sensitive and specific. The area under the receiver operating curves created using a range of white blood cell cut-offs was less than or equal to 0.6 for the presence of either type of infection, suggesting that such tests provide little additional information (i.e., a random guess would have a value of 0.5) [34]. Although specificity can be enhanced by the use of white blood cell cut-offs in concert with clinical findings of cervical erythema and mucopus, sensitivity of such testing remains poor, especially for chlamydia (sensitivity 41–52% for greater than or equal to 10 polymorphonuclear cells per high powered field) [35,36].

In men, urine leukocyte esterase testing has had variable sensitivity and specificity in the diagnosis of urethritis (Table 10.2), while the evaluation of urethral Gram stain findings for leukocytes has low sensitivity (~67%) for the presence of chlamydia [37].

In experienced hands, the use of urethral Gram stain for the identification of gram-negative diplococci appears to be an extremely sensitive and specific tool for the identification of gonorrhea in men. An extremely high degree of correlation between Gram stain results and nucleic acid amplification-based testing was reported in more than 7000 specimens submitted to a sexually transmitted disease program in Houston (kappa = 0.99) [38]. The ability to perform Gram stain evaluations on clinical specimens may markedly enhance the diagnostic usefulness of clinical algorithms, as described above. For example, in a study evaluating the diagnostic performance of an algorithm for urethritis, the addition of the Gram stain on urethral discharge markedly improved the specificity of algorithm diagnosis of gonorrhea (from 15% to 99%) [39].

The so-called "two glass test" (passage of about 50 mL of urine into the first glass, with the remainder passed into the second) has traditionally been used to distinguish infection in the anterior urethra from more proximal infection (anterior urethritis is thought to be present when only the first glass specimen has a cloudy appearance). The sensitivity and specificity of this test for the diagnosis of either gonococcal or chlamydial infection were 57% and 83% respectively in a cohort of Thai men [40].

Identification of individual pathogens

Recent years have seen an explosion in the use of molecular diagnostic tests, particularly nucleic acid amplification tests (NAAT), in the clinical diagnosis of STI. Commonly used NAAT include polymerase chain reaction (PCR), strand displacement amplification (SDA), and transmission-mediated amplification (TMA). NAAT not only improve test sensitivity in the diagnosis of STI caused by fastidious pathogens, but also permit the use of specimen collection techniques that overcome traditional barriers for STI testing. For example, newer tests may yield satisfactory results when specimens are obtained via self-sampling, which may increase test acceptability [41,42]. NAAT-based urine testing also has satisfactory sensitivity and specificity for the diagnosis of gonorrhea and chlamydial infection, such that the discomfort associated with

urethral swabs (in men) and speculum examination (in women) need no longer act as barriers to STI testing [43].

However, because newer tests may be more sensitive than the traditional "gold standards" (culture or microscopic visualization of an individual pathogen), calculation of sensitivity and specificity relative to a gold standard has become problematic. Furthermore, the use of additional tests to resolve discrepancies between negative culture tests and positive nonculture tests may introduce a form of verification bias, resulting in overestimation of sensitivity and specificity [44]. Such difficulties need to be taken into account in the interpretation of the data provided below. Emerging statistical methodologies, including latent class analysis and the use of composite reference standards, may improve future efforts to estimate test characteristics when gold standard tests are absent [45].

Neisseria gonorhoeae

Culture has long been considered the gold standard test for diagnosis of *N. gonorrhoeae* infections. The sensitivity of *N. gonorrhoeae* culture is relatively low in genital specimens when compared to nucleic acid amplification testing (Table 10.3) [46–49]. The poor sensitivity is due in part to loss of viability associated with delays in transport. A decline in sensitivity of culture testing from 89% to 78% was seen when onsite and off-site cultures were compared [48]. Specimen source also contributes to the sensitivity of culture, which is as low as 55% when specimens are obtained from the pharynx and 49% for rectal specimens [50,51].

More sensitive, nonculture methods for the diagnosis of gonococcal infection include nucleic acid hybridization ("probe") tests and NAAT. These tests have been the subject of a recent systematic review [52]. NAAT identified in this review were highly sensitive and specific in the diagnosis of gonococcal infections of the cervix (sensitivity 91–100%, specificity 97–100%), male urethra (sensitivity 98–100%, specificity 98–100%), and in male urine specimens (94–100%, specificity 98–100%). Studies of NAAT not included in this review have reported similar test characteristics [46,47,53–56]. Female urine specimens have demonstrated variable sensitivity for the detection of *N. gonorrhoeae* (65–91% sensitivity, specificity 99%) [43,53,55].

Although not approved for use on samples from nongenital sources, such as pharynx and rectum, certain NAAT have shown superior sensitivity compared to culture in the detection of *N. gonorrhoeae* in pharyngeal and rectal sites. A recent study demonstrated a sensitivity of 88% in the pharynx and 89–92% in the rectum. Specificity was consistently >97% [57].

Nucleic acid hybridization or "probe" tests were also highly sensitive and specific in the diagnosis of gonococcal infections of the cervix (sensitivity 91–100%, specificity 97–100%), male urethra (sensitivity 98–100%, specificity 98–100%), and in urine testing (94–100%, specificity 98–100%) [58,59].

Table 10.3 Estimated sensitivity of culture for *Neisseria gonorrhoea* relative to newer nucleic-acid-based tests

Population	Culture source	% Gonorrhea prevalence	% Sensitivity of culture (95% CI)	Reference
Female commercial sex-trade workers in Benin, South Africa, and Thailand	Endocervical	5	70 (57–81)	[46]
Male STD clinic attendees, Baltimore, Maryland	Urethral	22	77 (66–86)	[47]
Female STD clinic attendees, Baltimore, Maryland	Endocervical	18	65 (46–80)	[47]
Female hospital emergency department attendees, Omaha, Nebraska	Endocervical	7	89 (71–98)	[48]
Females using Duke University health system, North Carolina	Endocervical	4	93 (76–99)	[49]

Chlamydia trachomatis

Sensitivity of culture for the recovery of *C. trachomatis* is more limited than in *N. gonorrhoeae*, as the former must be grown in cell culture. Recovery is influenced by the expertise of the testing laboratory, composition of the collection swab, and timely transport to the microbiology laboratory. The limited sensitivity of culture has resulted in substantial efforts being devoted to the development of nonculture methods for the diagnosis of *C. trachomatis* infection. Such methods include antigen detection methods such as direct fluorescent antigen testing (DFA), enzyme immunoassay (EIA), and NAAT.

DFA and EIA perform with demonstrably lower sensitivity compared to culture and NAAT (though DFA still finds clinical application in the diagnosis of acute inclusion conjunctivitis related to vertical *C. trachomatis* infection in the newborn) [60,61]. NAAT have shown high sensitivity and specificity in the diagnosis of *C. trachomatis* infections of the cervix (sensitivity 90–94%, specificity 98–99%), in the male urethra (sensitivity 89–98%, specificity 96–99%), and in male urine testing (90–96%, specificity 94–98%). Sensitivity in female urine specimens has ranged from 81% to 95% [43,53,62,63].

Available evidence suggests that the sensitivity and specificity of certain NAAT for both *C. trachomatis* and *N. gonorrhoeae* detection using self-collected vaginal specimens are similar to that seen with clinician-collected cervical specimens [64]. Self-collection may have the advantage of greater acceptability or convenience in some circumstances [65–68]. The use of self-collected specimens may open the way to approaches such as mail-in sampling for population-based screening. In a study performed in general practices in Denmark, testing of pooled self-collected mail-in specimens had a sensitivity and specificity comparable to that seen with testing of pooled physician-collected cervical and urethral swabs (sensitivity 96–100%, specificity of 93–100% with self-collected specimens; sensitivity 91%, specificity 100% with clinician-collected specimens) [69].

Pelvic inflammatory disease

Clinical assessment remains the mainstay of diagnosis of pelvic inflammatory disease (PID), a spectrum of pathologic conditions including endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis. "Gold standard" tests (e.g., endometrial biopsy, laparoscopy) are invasive and not readily available in many clinical settings. The triad of lower abdominal discomfort, cervical motion tenderness, and adnexal tenderness has been suggested to represent minimal diagnostic criteria for PID [70].

A systematic review evaluated the sensitivity and specificity of historical, clinical, and laboratory findings for PID, when compared with laparoscopic diagnosis [71]. This review found no evidence that historical information (e.g., history of irregular menses or history of intrauterine device use) can reliably identify the presence of PID in cohorts of women with abdominal pain and other signs of genital tract infection. The presence of individual clinical signs, such as purulent vaginal discharge or a palpable adnexal mass on examination in an individual with a complaint of abdominal tenderness, was both insensitive and nonspecific [71]. In a study performed in Sweden in the 1960s, the presence of at least four clinical signs (such as pelvic tenderness, pelvic mass, fever, and abnormal vaginal discharge) was found to be specific (91%) for laparoscopically diagnosed PID but had a sensitivity of only 39% [72].

The detection of gonorrhea or chlamydia may be helpful in the diagnosis of PID in individuals with compatible signs and symptoms. In a study performed in a cohort of women with abdominal pain and tenderness on bimanual examination, the isolation of one of these organisms from the lower genital tract had a sensitivity and specificity of 77% for the presence of PID [73].

Two recent studies have used the presence of plasma cell endometritis, rather than laparoscopic evidence of PID, as the gold standard for the diagnosis of PID [74,75]. One study found the US Centers for Disease Control and Prevention (CDC) "minimal diagnostic criteria" to be only 33% sensitive for the presence of plasma cell endometritis, but 88% specific [74], while a second study found the CDC criteria to be more sensitive (83%) but less specific (22%) [75].

When available, ultrasonography may aid in the diagnosis of PID. The finding of fluid-filled fallopian tubes on ultrasound appears to be specific for the presence of PID, although the sensitivity of this finding has varied between studies (Table 10.4).

Table 10.4 Sensitivity and specificity of ultrasonographic detection of fluid-filled fallopian tubes in the diagnosis of pelvic inflammatory diseases

Population	Type of sonography	Study gold standard	% Sensitivity (95% CI)	% Specificity (95% CI)	Reference
51 nonpregnant outpatients in Helsinki, Finland	Transvaginal	Plasma cell endometritis on biopsy	85 (55–98)	100 (91–100)	[372]
30 consecutive individuals hospitalized for suspected PID in Helsinki, Finland	Transvaginal	Presence of PID at laparoscopy	81 (58–95)	78 (40–97)	[373]
55 women with suspected PID in Providence, Rhode Island	Transvaginal	Presence of PID at laparoscopy or histological endometritis on biopsy or culture of *N. gonorrhoeae* or *C. trachomatis* from upper genital tract specimen	32 (13–57)	97 (85–100)	[374]

Trichomonas vaginalis

Trichomomas vaginalis is a unicellular flagellated organism that causes vaginitis in women and urethritis in men. The importance of diagnosis and treatment relates to the association between infection with this organism and adverse outcomes in pregnancy, as well as enhanced HIV transmission [20,76]. A metaanalysis of test characteristics associated with simple bedside tests, such as the use of "wet mounts," and the use of Papanicolaou smear testing, found the sensitivity of these methods to be low (wet mount sensitivity 68%, 95% CI 62–74%; Papanicolaou smear sensitivity 58%, 95% CI 43–73%) [77].

Superior sensitivity is seen with other testing modalities, including culture and PCR-based testing. A systematic review and metaanalysis found that culture using special media has a sensitivity of 90% (95% CI 77–93%), while PCR has a sensitivity of 95% (95% CI 91–99%) and specificity of 98% (95% CI 96–100%) relative to culture. Other nonculture tests, including DFA testing (sensitivity 85%, specificity 99%) and ELISA (sensitivity 80–82%, specificity 73–98%) also have good test performance, and are less expensive than culture methods [78,79]. A novel ELISA-based "dipstick" can be used for diagnosis at the point of care [79].

The impact of delays in transport and inoculation onto special media on recovery of *T. vaginalis* by culture is controversial [80–82]. The relative expense of culture methods, but its superior test sensitivity relative to wet mount, has led to the suggestion that a two-step process might be more efficient, with inexpensive and highly specific "wet mount" testing used initially, and more expensive and sensitive tests reserved for specimens that test negative by wet mount [83]. It should be noted that such an approach would provide few advantages in settings where the prevalence of *T. vaginalis* infection is low. Another evolving facet of testing for trichomoniasis relates to the development of multiplex nucleic acid amplification tests which can be used to identify *T. vaginalis* as well as gonorrhea and *Chlamydia* with reasonable sensitivity and specificity [84].

Chancroid

Chancroid is an ulcerative genital disease caused by *Haemophilus ducreyi*. This organism has a distinct microscopic appearance, and direct Gram staining of purulent material from the ulcer base may reveal chains of short, gram-negative bacilli. Such a finding had a sensitivity of 60% compared with culture in a cohort of individuals with genital ulcer disease attending a sexually transmitted diseases clinic in Nairobi, Kenya [85]. Of 37 individuals who did not have *H. ducreyi* isolated by culture, 18 had Gram stain findings suggestive of *H. ducreyi*, suggesting either

lack of sensitivity of culture or lack of specificity of Gram stain. When compared with the use of concurrent PCR assays for *H. ducreyi*-specific sequences, culture for *H. ducreyi* had a sensitivity ranging from 63% to 87% [86–88].

Initial studies evaluating the use of PCR for the identification of *H. ducreyi* in clinical settings estimated sensitivity to be as low as 62% relative to culture [89]. However, subsequent technical improvements in specimen preparation have increased the sensitivity of PCR [90], and more current estimates of the sensitivity of PCR for detection of *H. ducreyi* range from 79–98%, with specificity of 92–100% relative to culture [87,88,91].

The use of PCR for the identification of *H. ducreyi* has provided important insights into the epidemiology of chancroid; for example, it has been observed that *H. ducreyi* may be present in ulcers coinfected with herpes viruses or *T. pallidum* [27–29,88]. Further, the phenomenon of asymptomatic carriage of *H. ducreyi* has been observed in 2% of commercial sex workers in the Gambia without signs or symptoms of chancroid [92].

Other diagnostic modalities, including an indirect immunofluorescent assay, and an enzyme immunoassay, may also have value in the diagnosis of chancroid [86].

Herpes simplex viruses

Herpes simplex viruses (HSV) are the most common agents of ulcerative genital disease in the developed world, and are increasingly recognized in the developing world as well [93]. Although genital herpes has traditionally been associated with HSV-2, recent studies from several industrialized world settings have shown that the incidence of genital HSV-1 infection has increased [94–96]. For instance, 78% of newly diagnosed genital herpes in a sample of US college students was attributable to HSV-1 [96]. However, HSV-2 accounts for the majority of recurrent genital herpes lesions because genital HSV-1 infection reactivates less frequently than HSV-2 [97,98].

The gold standard test for diagnosis of genital herpes has traditionally been culture of virus from genital lesions. If viral culture is not available, infection may be diagnosed by evaluating ulcer scrapings for the presence of multinucleated giant cells ("Tzank smear"). The sensitivity of Tzank smear relative to culture is 52–80% in anogenital lesions, with higher sensitivity in men than in women; the corresponding specificity is reported as 93% [99]. When used for orolabial herpes, the Tzanck smear has a reported sensitivity of 54% and a specificity of 100% relative to culture [100].

Enzyme immunoassays provide a rapid and sensitive alternative to culture for identification of HSV. The sensitivity of these tests has been estimated to be 80–96%, while their specificity has been reported as 93–100% [101–104]. Direct immunofluorescent assays may also be useful for the diagnosis of HSV in the genital tract, and provide a more timely diagnosis than culture. Reported sensitivity is 74–80%, and specificity is 85–98% relative to culture [105,106].

As has been noted, the quantification of the sensitivity and specificity of newer assays (e.g., nucleic acid amplification-based assays) is difficult, since these assays are more sensitive than culture, the traditional gold standard. For example, in studies using PCR as the gold standard, viral culture has a sensitivity of 72–88% [87,101,107,108], while EIA has a sensitivity of 65% [101]. A linear relationship exists between HSV detection by culture and the log copy number of HSV DNA detected by PCR, which may account for these differences [109]. In addition, the sensitivity of HSV culture relative to PCR may decline further if specimens are transported in warm weather conditions [109].

Older serologic assays for anti-herpes simplex antibody were unable to reliably distinguish between infection with HSV-1 and HSV-2 [110]. More recent serologic assays, such as glycoprotein G-based Western blot, can differentiate the response to infection with these two viruses, and are more than 90% sensitive if performed 21 days or more after primary infection [111]. Based on individuals prospectively followed in the setting of randomized controlled trials, it can be estimated that approximately 40% of those who acquire HSV-2 infection (as evidenced by seroconversion) actually develop genital herpes [112].

Newer FDA-approved, ELISA-based assays for type-specific antibodies against HSV-1 and HSV-2 such as HerpeSelect™ 1 and 2 (Focus Technology, Inc., Herndon, Virginia) have reported sensitivities and specificities of 96–100% and 97–100% respectively [113,114] when compared with Western blot assays, and are less expensive to perform. The role of antibody testing in the diagnosis of genital herpes remains

poorly defined, but such tests might be used in diagnosing recurrent or atypical symptoms with negative culture results [115], in counseling couples [116], and in pregnancy-related screening [117,118].

Syphilis

Primary and secondary syphilis may be diagnosed by visualization of spirochetes from ulcers, condylomata lata, and mucous patches using dark-field microscopy. Such diagnostic methods require both technical competence and experience; in the hands of an experienced microscopist, the sensitivity of dark-field microscopy has been estimated to range from 74% to 81% when compared with various reference standards [87,119–121]. The finding of motile spirochetes by dark-field microscopy in a sample from a genital lesion might be expected to be pathognomonic for syphilis, but other nonpathogenic genital tract spirochetes may lead to false-positive test results [122]. Antibody-based assays and PCR may also be used to detect the presence of *T. pallidum* in lesions of primary or secondary syphilis, and may offer improved sensitivity in detection of treponemes (Table 10.5).

Serologic testing is the mainstay of syphilis diagnosis in adults with nonprimary disease; the characteristics of these tests have been reviewed in detail elsewhere [122,123]. Such tests can be classified as nontreponemal tests, which identify antibodies not directed against treponemes, and treponemal tests, which identify antibodies directed at treponemal components. Nontreponemal tests may be positive in the presence of a primary chancre, but are less than 90% sensitive in primary syphilis. Sensitivity is higher in secondary and early latent syphilis. By contrast, the fluorescent treponemal antibody absorbed assay (FTA Abs), a treponemal test, is usually positive within a week of the development of a primary chancre (Fig. 10.2).

A small proportion of individuals with syphilis have a negative nontreponemal test for syphilis due to "prozone" phenomena, which occur when extremely high titers of antibody disrupt the assay. This results in a false-negative test result, which becomes positive upon dilution [124]. Nontreponemal tests revert to negative over time in approximately 30% of untreated individuals [125]; treponemal tests may uncommonly revert to negative, a phenomenon that appears to be more common in individuals with HIV-associated immune dysfunction [126].

The specificity of nontreponemal tests is problematic, and reports of falsely positive nontreponemal tests in the presence of other infectious diseases, rheumatologic diseases, and pregnancy are common [127]. The relative risk of a false-positive nontreponemal test in individuals with underlying HIV infection was 8.4 (95% CI 4.2–13.6) in a Spanish cohort [128]. Nonetheless, nontreponemal tests remain useful as screening tests because of their low cost, and because a reduction in titer following treatment is a useful indicator of microbiologic cure [129]. Treponemal tests are more specific than nontreponemal tests, although false-positive test results are reported [127]. Treponeme-specific tests, such as syphilis ELISA and TPHA, can be used for automated, high-throughput testing [130,131], but this does not obviate the need for both confirmatory testing, and the ongoing use of nontreponemal tests, which can identify reinfection and which can be used to evaluate response to treatment [132]. Interpretation of results with reactive treponemal tests and negative nontreponemal test require a detailed clinical and epidemiologic history as well as physical examination to appropriately integrate the serologic result into the clinical picture. The notable disadvantage of serologic testing in nonprimary syphilis is the lack of a true gold standard test; this is particularly important in asympomatic patients and especially the patient with HIV coinfection. The characteristics of commonly used laboratory tests for the serologic diagnosis of syphilis are presented in further detail in Table 10.6.

In an effort to combat high rates of congenital syphilis in the developing world, rapid point-of-care syphilis tests have come into focus as a method of increasing access to onsite diagnosis (and targeted treatment). Sensitivity of these tests (compared to TPHA or TPPA) appears higher when used with whole blood (84–96%) than with serum (where sensitivity has been as low as 57%) [133]; specificity has been >95%. Sensitivity may also be worse in the field than in laboratory conditions [134]. Although empiric data on cost-effectiveness are not available, model-based estimates suggest that using these tests to target antimicrobial therapy may prevent congenital syphilis at a cost of $0.22 per case averted, a ratio that would be considered highly cost-effective in the developing-world context [135].

The diagnosis of neurosyphilis is challenging. While VDRL testing of cerebrospinal fluid (CSF VDRL)

Table 10.5 Diagnostic characteristics of commonly used tests for the detection of *Treponema pallidum* in early syphilis

Population or specimen source	Prevalence (%)	Comparator or study gold standard	Sensitivity (%)	Specificity (%)	Reference
Darkfield microscopy					
128 individuals with anogenital lesions attending an STD clinic in Edmonton, Alberta	52	Positive darkfield evaluation or positive serologic test for syphilis	79	100	[121]
350 specimens taken from individuals with lesions suggestive of syphilis (>1 specimen per individual)	34	"Subsequent diagnosis of syphilis"	74	97	[120]
302 individuals with genital ulcer disease in Pune, India	14	Multiplex PCR	39	82	[28]
188 individuals with genital lesions attending STD clinics in Brooklyn, New York, and Seattle, Washington	34	Direct fluorescent monoclonal antibody testing	85	96	[119]
295 men presenting to New Orleans sexually transmitted diseases clinic with genital ulcer	25	Multiplex PCR	81	100	[87]
241 individuals assessed at county clinics in San Francisco and Los Angeles with lesions suggestive of primary syphilis	22	Direct fluorescent antibody testing	85	97	[375]
Direct fluorescent antibody test					
241 individuals assessed at county clinics in San Francisco and Los Angeles with lesions suggestive of primary syphilis	18	Darkfield microscopy	86	93	[375]
156 individuals with genital ulcer disease from Malawi	17	PCR with dot-blot hybridization	85	97	[376]
128 individuals with anogenital lesions attending an STD clinic in Edmonton, Alberta	52	Positive darkfield evaluation or positive serologic test for syphilis	79	100	[121]
350 specimens taken from individuals with lesions suggestive of syphilis (>1 specimen per individual)	34	"Subsequent diagnosis of syphilis"	86	100	[120]
188 individuals with genital lesions attending STD clinics in Brooklyn, New York, and Seattle, Washington	34	Darkfield microscopy	91	93	[119]
PCR					
295 men presenting to New Orleans sexually transmitted diseases clinic with genital ulcer	22	Darkfield microscopy	100	99	[87]
301 individuals tested for early syphilis in sexual health clinics in Melbourne, Australia	17	Concurrent serological testing for syphilis	80	98	[377]

Continued

Population or specimen source	Prevalence (%)	Comparator or study gold standard	Sensitivity (%)	Specificity (%)	Reference
98 individuals (86 male) with clinical signs and symptoms resulting in testing for syphilis at UK genitourinary medicine clinics	29	Diagnosis by clinicians, with consideration of all laboratory results (including serology)	95	99	[378]
112 individuals attending a public sexual health clinic in Amsterdam with suspected syphilis. Compared 3 different PCR-based assays	12	Darkfield microscopy and serology	94–100	99–100	[379]

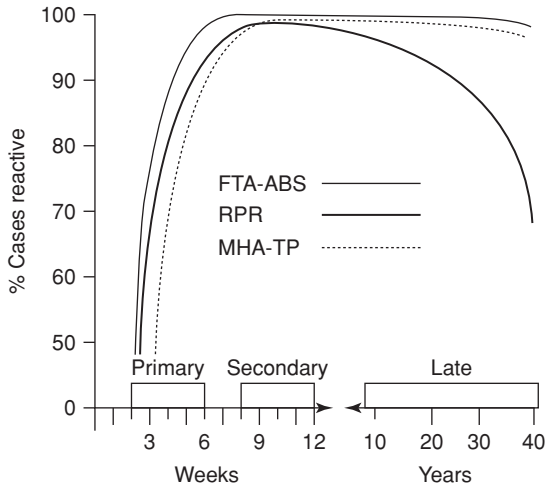


Figure 10.2 Timing of serologic test positivity in syphilis. Comparison of timing of test positivity for a nontreponemal test (rapid plasma regain or RPR), and two treponemal tests (fluorescent treponemal antibody absorbed (FTA-ABS) and microhemagglutination assay for *T. pallidum* (MHA-TP)). Both the RPR and FTA-ABS are positive in most individuals with a primary chancre, but FTA-ABS is more sensitive in primary syphilis. The two treponemal tests remain positive over time, while RPR will revert to negative in approximately one-third of untreated individuals. Reproduced from reference [122]: Larsen SA, Steiner BM, Rudolph AH. Laboratory diagnosis and interpretation of tests for syphilis. Clin Microbiol Rev 1995;8(1):1–21 with permission from the American Society for Microbiology.

is often advocated, the sensitivity of this test is poor. A retrospective study was performed in 38 individuals with positive cerebrospinal fluid FTA-Abs (a test thought to be sensitive but nonspecific for the diagnosis of neurosyphilis). Fifteen of 38 had likely neurosyphilis on the basis of a compatible clinical history and other CSF abnormalities (e.g., leukocytosis or elevated protein), but only four of these 15 individuals had a positive CSF VDRL (sensitivity 27%) [136].

The use of the "TPHA index" has been suggested as a more sensitive means of diagnosing neurosyphilis. This index is based on an antibody test (MHA-TP) that is more sensitive than CSF VDRL. False-positive test results are reduced by adjusting for CSF protein concentration, which in turn helps to control for blood contamination of the CSF sample [137]. However, a study in individuals coinfected with HIV and syphilis found high index values in only five of 40 individuals with possible neurosyphilis, and three of five individuals with positive CSF VDRL tests, suggesting that the TPHA index may also be relatively insensitive for active central nervous system infection [138].

Existing evidence does not support the routine use of PCR for the diagnosis of neurosyphilis in adults, and published studies have yielded inconsistent results [139,140]. In a study conducted in infants born to mothers with untreated syphilis in Dallas, Texas, CSF PCR had a sensitivity of 65% when compared with a gold standard of rabbit infectivity testing; in this study PCR of blood or serum was more sensitive than CSF

Table 10.6 Ranges of sensitivity and specificity reported for serological tests for syphilis by stage

	Sensitivity (%)					
Test	**Primary**	**Secondary**	**Latent**	**Late**	**Specificity (%)**	**Reference**
Nontreponemal tests						
VDRL	74–87	100	88–100	34–94	96–99	[125,380,381]
RPR	77–100	100	95–100	73	93–99	[125,381]
TRUST	77–86	100	95–100	–	98–99	[125]
USR	72–88	100	88–100	–	99	[125]
Treponemal tests						
FTA-ABS	70–100	100	99–100	96	84–100	[125,380–382]
MHA-TP	69–90	99–100	97–100	94	98–100	[125,380–382]
Nonstandard tests						
ELISA	82–100	91–100	86–100	100	89–100	[130,383–387]
Western blot	78–100	98–100	83–100	100	97–100	[388–390]

VDRL, Venereal Disease Research Laboratory; RPR, Rapid Plasma Reagin; TRUST, toluidine red unheated serum test; USR, unheated serum reagin; FTA-Abs, fluorescent treponemal antibody absorbed; MHA-TP, microhemagglutination assay for T. pallidum; ELISA, enzyme-linked immunosorbent assay.

PCR for the presence of central nervous system disease (94%) [141].

Diagnosis of genital warts and human papillomavirus infection

The diagnosis of genital warts is usually made clinically, but rigorous studies of the sensitivity and specificity of clinical diagnosis are lacking. Although the intuition of experienced clinicians was more sensitive and specific than the use of a standardized diagnostic instrument in a small study of extragenital warts, the gold standard used in this study was the clinical judgment of one of the study investigators [142].

Acetic acid (3–5%) has been used as an adjunct to the clinical diagnosis of genital warts, and whitening with acid application is said to signify the presence of underlying HPV infection. The application of acetic acid has also been advocated for the identification of subclinical warty lesions. However, whitening appears to be nonspecific for the presence of HPV infection: in a cohort of Swedish army conscripts, HPV DNA was detected by PCR in only 17 of 39 biopsy specimens taken from aceto-white areas, and there was no difference in the detection of HPV DNA in urethral brushings from men with and without aceto-white lesions [143]. In another study HPV DNA was detected in only 55 of 91 acetowhite lesions detected by penoscopy, with other aceto-white biopsy specimens having histology suggestive of eczema [144].

Furthermore, aceto-white lesions appear to be insensitive for the presence of HPV infection: in a cohort of Swedish women undergoing colposcopy, the finding of an aceto-white vulvar lesion had a sensitivity of 44% for the detection of HPV DNA by PCR [143]. Finally, many clinically typical genital warts do not turn white with the application of acetic acid. In a study of 202 men in Chandigarh, India, all hyperplastic warts turned white with the application of acetic acid, but only one of 12 typical verruca vulgaris-type lesions, and 15 of 59 flat warts, did so [145]. Thus, the poor sensitivity and specificity of acetic acid testing for small or subclinical genital warts, combined with the lack of evidence to suggest that treatment of such lesions changes long-term outcome, makes it difficult to advocate the routine use of acetic acid testing for external genital warts.

Similarly, no evidence exists currently to support the use of HPV DNA testing in the clinical diagnosis of external genital warts. However, such testing may contribute substantially to cervical cancer screening programs. The presence of "high-risk" HPV DNA in genital tract specimens of women with atypical squamous cells of undetermined significance (ASCUS)

on Papanicolaou smear is highly sensitive for the presence of underlying cervical neoplasia [146–148]. Mathematical models based on available screening data suggest that the incorporation of HPV DNA testing into screening practices would likely be cost-effective relative to current practices [149–151]. A more complete review of the relationship between human papillomavirus and cervical neoplasia is available elsewhere [152].

Prevention of STI

Condoms and other contraceptives

Evidence exists to support the effectiveness of latex male condoms in preventing transmission of several different STI. A prospective study of the impact of condom use on acquisition of either HIV or other STI in a community in Uganda found consistent condom use to be associated with a reduced risk of acquiring HIV infection (RR 0.4, 95% CI 0.2–0.9), syphilis (OR 0.7, 95% CI 0.5–0.9), and gonorrhea or chlamydia (OR 0.5, 95% CI 0.3–1.0). These effects were seen despite the fact that condom users had riskier sexual practices than nonusers [153]. No reduction in risk was associated with inconsistent condom use. Another prospective cohort study in a cohort of Kenyan sex trade workers found consistent condom use to be associated with a decreased risk of chlamydia (HR 0.6, 95% CI 0.4–0.9); gonorrhea (HR 0.6, 95% CI 0.4–0.8), genital ulcer disease (HR 0.5, 95% CI 0.3–0.9), and PID (HR 0.6, 95% CI 0.4–0.9), after adjustment for such covariates as place of work and number of sexual encounters per week [154]. A prospective study in American sailors suggested that consistent condom use reduced the risk of gonorrhea acquisition during shore leave from 10% to 0%, although this difference was not statistically significant, perhaps as a result of the small number of sailors who actually reported using condoms [155].

The relationship between condom use and acquisition of genital herpes was studied in the context of a trial of a herpes vaccine in couples discordant for genital infection with HSV-2. Condom use by males during sexual intercourse in 25% of episodes or more was associated with a dramatic reduction in the hazard of acquisition of genital herpes by female partners (adjusted HR 0.09, 95% CI 0.01–0.7) [156]. No effect was seen on female-to-male transmission in this study, but the study likely lacked statistical power to find such an effect. A more recent cohort study found "frequent" condom use to decrease the risk of HSV-2 acquisition in both males and females (HR 0.74, 95% CI 0.59–0.95) [157].

A systematic review and metaanalysis evaluated the relationship between condom use and acquisition of HPV infection, or HPV-associated disease (e.g., genital warts or cervical intraepithelial neoplasia). The authors found no convincing evidence for a protective effect associated with condoms [158]. However, a more recent cohort study in newly sexually active university students identified a strong protection against HPV acquisition associated with consistent condom use (adjusted HR 0.3, 95% CI 0.1–0.5); condom use also reduced the incidence of cervical intraepithelial neoplasia [159]. Similar findings were reported in a recent study of HPV transmission in infection-discordant couples [160].

Other contraceptive practices, including the use of spermicides, oral contraceptive pills, and intrauterine contraceptive devices (IUD), may affect the risk of STI. Despite the fact that it is bactericidal in vitro, there is no consistent evidence to suggest that the spermicide nonoxynol-9 reduces the risk of genital gonorrheal or chlamydia infection [162–166]. Further, nonoxynol-9 may increase the risk of ulcerative genital disease, which may enhance HIV transmission [163,166].

A strong association between IUD and PID was noted in a multicenter case–control study conducted in the late 1970s [167], but subsequent analyses found the risk of PID to be most strongly associated with one particular type of IUD, the "Dalkon shield" (OR 15.6; 95% CI 8.1–30.0). The association of other types of IUD with PID is more controversial [168–173].

Hormonal contraception, particularly oral contraceptive pills, may enhance the risk of acquisition of cervicitis, particularly due to *C. trachomatis* [154], but a number of studies have found that symptomatic PID associated with *C. trachomatis* is less likely in women who use oral contraceptive pills [174,175]. This paradox may relate to the impact of oral contraceptive pills on recognition of PID: in a case–control study, individuals with asymptomatic PID were found to be 4.3 times as likely to use oral contraceptives as women with symptomatic disease (95% CI 1.6–11.7) [176].

Management of sexually transmitted infections

Case presentation (continued)

The male adolescent described above is treated syndromically for urethritis with 1 g of oral azithromycin, and 400 mg of oral cefixime. Because of the presence of abdominal discomfort, adnexal tenderness, and cervical motion tenderness, his female partner is treated for PID. Despite some misgivings related to the question of compliance, the treating physician opts to manage her as an outpatient, with a 2-week course of oral metronidazole and levofloxacin. Subsequent laboratory testing shows both to be infected with *Chlamydia trachomatis* as well as gonorrhea. The female patient subsequently fails to return for scheduled follow-up; when contacted by local public health personnel 2 weeks after presentation, she says that she took "all her medication," although she is still experiencing vaginal discharge and low abdominal discomfort. You wonder.

- How effective is syndromic management of STI?
- How effective is directed treatment of STI?
- Does treatment of sexual partners reduce the risk of relapse or reinfection?
- Are population-based interventions (including vaccination, screening, the use of mass antibiotic treatment) effective as control strategy for STI?
- Can behavioral interventions modify the future risk of sexually transmitted infection?

As discussed above, the syndromic diagnosis of STI is substantially less accurate than laboratory-based diagnosis. Nonetheless, evidence exists to support management based on syndromic diagnoses, as this approach results in receipt of treatment by most infected individuals, and eliminates concerns related to nontreatment as a result of loss to follow-up.

For example, despite the lack of accuracy of the clinical diagnosis of cervicitis, a study performed in female sex trade workers in Benin found that such a diagnosis was sufficient to warrant treatment for gonorrheal and chlamydial infections. The clinical diagnosis of cervicitis in this study was 48% sensitive and 75% specific for the presence of gonorrhea or chlamydia. This compared unfavorably to the 75% sensitivity and 100% specificity associated with laboratory diagnosis. However, the "effective sensitivity" of laboratory diagnosis, defined as the proportion of infected individuals detected by laboratory testing who actually returned to clinic within 30 days, was only 29%, worse than that seen with clinical diagnosis alone [177].

A single non-randomized, controlled clinical trial has compared outcomes following the use of a diagnostic algorithm (with speculum examination) to a diagnostic approach incorporating basic microbiologic testing in the evaluation of vaginal discharge. In this study, performed in a cohort of women in southern Thailand, the presence of gross cervical mucopus was a less sensitive indicator of cervical infection with gonorrhea and chlamydia than was the finding of microscopic mucopus on Gram stain (sensitivity 34% vs 64%). However, no significant differences were seen between groups in the proportion of women with gonococcal or chlamydial infection at follow-up, or in the proportion of women with persisting vaginal discharge 1–2 weeks after initial evaluation [178]. It should be noted that this study may have lacked statistical power to detect clinically significant differences in outcome.

Intensified syndromic management of STI has also been evaluated as a strategy for preventing HIV infection in two East African trials. In a randomized controlled trial of pairwise matched communities in Mwanza district, Tanzania, a strategy including syndromic STI treatment resulted in a slight, but nonstatistically significant, decrease in prevalence of syphilis (adjusted RR 0.92, 95% CI 0.78–1.07) and gonorrhea/chlamydia (adjusted RR 0.65; 95% CI 0.26–1.62), and successfully reduced HIV incidence (RR 0.58, 95% CI 0.42–0.79) [179]. In a cluster-randomized controlled trial in the Masaka district of Uganda, a similar syndromic STI management strategy decreased the incidence of syphilis (IRR 0.52, 95% CI 0.27–0.98) and prevalence of gonorrhea (PR 0.25, 95% CI 0.10–0.64), but had no impact on HIV incidence (IRR 1.00, 95% CI 0.63–1.58) [180]. The apparently contradictory results of these and other studies regarding HIV incidence have been attributed to epidemiologic differences in the stage of the HIV epidemic, as well as differences in prevalence of HSV-2 infection (see below) [180].

Treatment of *Neisseria gonorrhoeae* infections

A variety of drug regimens for the treatment of uncomplicated gonococcal urethritis and cervicitis

have been assessed since the late 1960s via randomized controlled trials [181–183]. However, the relevance of early trials to current practice is limited, owing to the emergence of widespread antibiotic resistance in *N. gonorrhoeae*. Resistance to penicillins, tetracyclines, and macrolides have become commonplace throughout the world [184,185]. Although tetracycline and penicillin resistance have actually diminished in some areas in recent years, this probably reflects decreased selective pressure because of the nonuse of these agents by treating clinicians [184].

Prior to the emergence of widespread β-lactam resistance, the use of a single 3 g oral dose of ampicillin or amoxicillin, combined with 1 g of probenecid, was highly effective for the treatment of uncomplicated gonorrheal infections [182]. However, a randomized controlled trial performed in an area of Ethiopia with high rates of penicillin resistance demonstrated that in vitro resistance to penicillin was associated with clinical treatment failure; 19% of individuals treated with oral ampicillin and probenecid experienced clinical failure, while no failures were noted with a single 2 g intramuscular dose of spectinomycin [186].

A subsequent randomized trial in Thailand showed single-dose therapy with third-generation cephalosporins to be equivalent in efficacy to single-dose spectinomycin therapy [187]. Treatment with either a single 400 mg dose of cefixime orally, or 250 mg of ceftriaxone intramuscularly, reliably cured more than 95% of individuals with uncomplicated gonococcal urethritis or cervicitis in a randomized controlled trial performed in Nairobi, Kenya [188]. Single-dose cefixime and ceftriaxone have also been found to be highly effective and equivalent in a randomized controlled trial performed in the US [189].

Fluoroquinolones may be useful agents as single-dose therapy for uncomplicated gonococcal infections in some geographic areas. A US trial completed in the 1980s found single-dose ofloxacin (400 mg) to be equivalent to therapy with amoxicillin plus probenecid [190]. Comparison of a single 500 mg dose of ciprofloxacin with intramuscular ceftriaxone for urethritis treatment in an area of Zambia with a high prevalence of antibiotic-resistant *Neisseria gonorrhoeae* found the two treatment regimens to be equivalent [191]. However, resistance to fluoroquinolones has recently become widespread in many parts of the world [192,193]. The US CDC issued an advisory in 2007 indicating that fluorquinolone use should be avoided altogether for treatment of gonorrhea [194], leaving cefixime and ceftriaxone as the sole recommended agents for empiric treatment of *N. gonorrhoeae* infections in the US. There is strong evidence linking in vitro resistance to fluoroquinolones to clinical treatment failure. A randomized controlled trial compared the efficacy of ceftriaxone to that of ciprofloxacin in *N. gonorrhoeae*-infected sex-trade workers in the Philippines. The relative risk of clinical failure when individuals with a highly fluoroquinolone-resistant organism (defined by ciprofloxacine MIC greater than or equal to 0.4 μg/mL) were treated with ciprofloxacin was 13.1 (95% CI 1.8–93.0) [195].

A single 2 g dose of azithromycin may be an effective treatment for uncomplicated gonococcal infection. In a randomized trial both azithromycin and a single 250 mg intramuscular dose of ceftriaxone eradicated gonorrhea in more than 97% of participants; concomitant chlamydial infection was eradicated by azithromycin, but not by ceftriaxone [196]. The effectiveness of azithromycin outside the context of a clinical trial may be limited by the fact that over a third of trial participants experience gastrointestinal discomfort with high-dose azithromycin, and by the emergence of azithromycin resistance in gonococcal solates [197]. Although resistance to spectinomycin and third-generation cephalosporins remains uncommon, resistance to these agents has been reported and may increase in coming years [198]. Because of the extremely dynamic nature of antimicrobial resistance in *N. gonorrhoeae*, clinicians should remain abreast of changes in antimicrobial resistance patterns; in North America, an excellent resource in this regard is the Gonorrhea Isolate Surveillance Project (GISP) (http://www.cdc.gov/std/GISP/default.htm).

Treatment of *Chlamydia trachomatis* infections and nongonococcal urethritis or cervicitis

The past three decades have seen an evolution in the understanding of so-called nongonococcal urethritis, postgonococcal urethritis, and mucopurulent cervicitis, with increasing recognition that these syndromes are most commonly caused by *C. trachomatis*. As such, early data on the treatment of chlamydial infections are derived from studies that did not explicitly identify this pathogen, or which grouped chlamydial

infections with those caused by other nongonococcal organisms.

The efficacy of tetracyclines in the treatment of chlamydial infections has been demonstrated in several randomized controlled trials. An early trial compared spectinomycin to tetracycline for the treatment of gonorrhea, and found postgonococcal urethritis to occur less frequently with tetracycline [178]. Tetracyclines were subsequently found to be superior to sulfa drugs combined with spectinomycin in a randomized trial in men with nongonococcal urethritis [199]. Doxycycline was also significantly more efficacious than placebo in preventing postgonococcal urethritis (RR 0.6, 95% CI 0.4–0.8) [200].

Minocycline (100 mg twice daily), doxycycline (100 mg twice daily), and tetracycline (250 mg four times a day) had equal efficacy in the treatment of nongonococcal urethritis and mucopurulent cervicitis in randomized trials [201,202]. A 2 g total daily dose of tetracycline may be more efficacious than a single gram total dose [203].

Macrolide agents serve as a valuable alternative to the tetracyclines for the treatment of chlamydial infections. A week of therapy with 1 g per day of either erythromycin or tetracycline had equal efficacy in a randomized trial of treatment for men with chlamydial urethritis and their infected sex partners [204], and newer macrolides such as clarithromycin (250 mg twice daily for 7 days) and roxithromycin (300 mg once a day for 10 days) also appear to be equivalent to doxycycline in the treatment of uncomplicated genital chlamydia infections and nongonococcal urethritis and cervicitis [205,206].

The development of azithromycin has had a dramatic impact on the treatment of chlamydial infections in the clinic setting, with a single 1 g dose of azithromycin proved equivalent to a 7-day course of doxycycline in the eradication of chlamydial infection, and in the resolution of cervicitis and urethritis. A systematic review and metaanalysis of 12 randomized controlled trials comparing azithromycin and doxycycline for the treatment of urethritis or cervicitis found no difference between these regimens in microbiologic cure, or in the incidence of adverse drug events [207].

Fluoroquinolones have had variable efficacy in the treatment of chlamydial infections. Two randomized trials comparing ciprofloxacin (750–1000 mg twice daily) to doxycyline found that elimination of chlamydia occurred in only 46–62% of those treated with ciprofloxacin, in contrast to 75–100% of those treated with doxycycline [208,209]. In contrast, one week of ofloxacin at a dose of 300–400 mg twice daily appears to be equivalent in efficacy to doxycycline dosed at 100 mg twice daily, with both drugs reported to eradicate chlamydial infections in 97–100% of individuals with urethritis or cervicitis [208,209]. Newer quinolones, such as sparfloxacin, grepafloxacin, and trovafloxacin, have been proven efficacious for the treatment of uncomplicated chlamydial infections of the genital tract, but their use has been limited by severe adverse drug effects, including cardiac arrhythmias and hepatotoxicity [210–212].

Untreated lower genital tract chlamydial infection appears to be associated with adverse pregnancy outcomes including prematurity, low birthweight, stillbirth, postpartum endometritis, and pneumonitis and conjunctivitis in the newborn [213–221]. A retrospective cohort study found lower perinatal mortality associated with erythromycin treatment versus no treatment in pregnancies with a positive chlamydial culture [222]. A second retrospective cohort study found that women with successfully treated chlamydial cervicitis had lower frequencies of premature rupture of membranes and small-for-gestational-age infants compared with unsuccessfully treated women [22]. A randomized placebo-controlled trial evaluating chlamydia screening and erythromycin treatment in pregnancy found no differences between study arms, but this absence of effect may have occurred as a result of high rates of ancillary antibiotic use in the placebo arm [223].

Subsequently, randomized controlled trials have compared amoxicillin (500 mg three times a day for 7 days) to nonestolate preparations of erythromycin for the treatment of uncomplicated chlamydial infection in pregnant women. A metaanalysis of trials comparing amoxicillin and erythromycin found the two drugs to be similar in efficacy, although amoxicillin is associated with a lower incidence of adverse effects, especially nausea [224]. With increasing comfort related to the use of azithromycin in pregnancy, randomized trials have been performed comparing this agent to amoxicillin; the two agents appear to have equivalent efficacy [225,226].

Treatment of pelvic inflammatory disease

The agents of urethritis and cervicitis are strongly associated with the development of PID, a syndrome

characterized clinically by the presence of lower abdominal pain, cervical motion tenderness, and uterine adnexal tenderness. However, while either *N. gonorrhoea* or *C. trachomatis* or both organisms are identifiable in cervical culture specimens of 70% of individuals with clinically diagnosed PID, this infection is typically polymicrobial, and therapeutic regimens include agents that are effective against these organisms, as well as gram-negative bacilli and anaerobes. A systematic review of 34 clinical trials and case series found most available drug regimens to be associated with cure in 80–100%, although the pooled probability of cure was less than 80% when doxycycline and metronidazole were used without other agents [227].

A key clinical branch point in the management of PID involves the question of whether individuals need to be admitted to hospital for therapy. A single randomized controlled trial (the "PEACH" trial) evaluated the question of inpatient versus outpatient therapy for women with moderate PID diagnosed clinically: 831 women received inpatient treatment with intravenous cefoxitin and doxycycline, or outpatient treatment with a single intramuscular injection of cefoxitin and oral doxycycline. No significant differences were seen in short-term cure rates, or in the development of longer-term sequelae, including infertility, pelvic pain, and ectopic pregnancy in the 808 women available for long-term follow-up. The average follow-up time in these women was 35 months [228].

Treatment of syphilis

Benzathine penicillin and aqueous penicillin G are the mainstays of therapy for syphilis, and are believed to be highly effective despite a lack of randomized controlled trials. Evidence supporting the use of tetracyclines as an alternative to penicillin for syphilis treatment is similarly based on descriptions of case series [229,230]. Recent randomized controlled trials of therapy for syphilis have compared alternative treatments to penicillin-based regimens.

Intramuscular ceftriaxone is commonly used as an alternative to benzathine penicillin for syphilis not affecting the central nervous system; however, there is little in the clinical trials literature to support this practice. A small randomized controlled trial compared a 15-day course of intramuscular penicillin to 1 g of intramuscular ceftriaxone given every other day for 7 days (i.e., four doses in total) in 28 patients with early syphilis. This study found an adequate serologic and clinical response in all participants [231]. A small randomized controlled trial comparing a single 2.4 million unit dose of benzathine penicillin to a single 3 g intramuscular dose of ceftriaxone and to 2 g of ceftriaxone given intramuscularly for 5 days found either clinical cure or sustained clinical response in 16 of 17 participants available for follow-up. Although the single failure of treatment occurred with single-dose ceftriaxone, this study was too small to permit comparisons between treatment regimens [232].

A promising alternative to benzathine penicillin in the treatment of early syphilis was azithromycin, which when compared with benzathine penicillin in an open-label pilot study [233] had provided promising results. A total of 74 patients were randomized to receive standard dose benzathine penicillin, a single 2 g dose of azithromycin, or two 2 g doses of azithromycin 1 week apart. Of the 46 individuals available for evaluation a year after therapy, only three had experienced serologic evidence of relapse or failure of response (defined as a $<$2-fold reduction in RPR titers from pretreatment levels). In a similar study conducted in Tanzania, patients with primary or high-titre (RPR $>$ 1:8) latent syphilis were randomized to benzathine penicillin 2.4 million units intramuscularly as a single dose or to a single oral dose of 2 g of azithromycin. At 9 months of follow-up, cure rates were equivalent.

However, the value of azithromycin for treatment of syphilis is threatened by the emergence of antimicrobial resistance in the US, Ireland, and Canada [234–236]. Treatment failure with azithromycin was first documented in San Francisco in 2002, when three patients with primary syphilis did not respond to azithromycin treatment, and five patients who were contacts of patients with early syphilis experienced clinical symptoms or seroconversion. Molecular evidence indicated that the A2058G mutation (previously linked to erythromycin resistance) conferred azithromycin resistance in *T. pallidum* [234]. Although surveillance for azithromycin resistance is in its infancy, in San Francisco, the proportion of specimens that harbor the resistance mutation has increased from 41% of 32 isolates in 2003, to 77.3% of 22 isolates in 2006 [234].

Case reports and series suggesting that HIV-infected individuals are more prone to relapse after

treatment of syphilis with standard drug regimens [237,238] prompted investigators to initiate two randomized controlled trials comparing usual therapy with penicillin to alternate therapies. The first of these trials [239] compared a standard regimen of 2.4 million units of benzathine penicillin G intramuscularly with standard therapy plus a 10-day course of amoxicillin and probenicid in 541 individuals with primary, secondary, or early latent syphilis: 101 participants were HIV-infected, with one-third of these having very low CD4 cell counts. No differences were seen between groups in clinical outcomes, regardless of HIV status or treatment regimens. A second trial compared 10 days of intramuscular ceftriaxone (2 g per day) to aqueous penicillin G (24 million units per day) in 36 individuals with neurosyphilis and HIV coinfection [240]. No difference was seen in the proportion of individuals with improvement in CSF VDRL titers, white blood cell counts, or protein concentrations at 14–26 weeks after therapy, although ceftriaxone was associated with a greater decline in serum RPR titers.

Preventive therapy is usually recommended for sex contacts of individuals found to have infectious syphilis. A randomized, open-label trial compared azithromycin to benzathine penicillin for the prevention of syphilis in individuals with an infectious sex partner. None of the 96 participants was documented to have developed syphilis during follow-up, although fully one-third of participants were lost to follow-up before completing 3 months of post-treatment surveillance [241]. Syphilis incidence also appears to be reduced in cohorts treated for gonorrhea with tetracyclines or erythromycin, suggesting that these agents are also effective against incubating syphilis [242].

Intravenous penicillin G or intramuscular procaine penicillin have been recommended for the treatment of infants with clinical illness related to congenital syphilis [243]. However, a randomized controlled trial comparing a single dose of benzathine penicillin to a 10-day course of intramuscular procaine penicillin in 169 infants with asymptomatic congenital syphilis found no differences in efficacy between the two drug regimens. All 152 infants available for follow-up at 2–3 months had a 4-fold decrease in RPR titers, while 149 became RPR nonreactive [244]. A small clinical trial performed in South Africa randomized asymptomatic infants of mothers with untreated syphilis and high serum regain titers to single-dose benzathine penicillin or no therapy. While this study raises ethical concerns, it clearly demonstrated that nontreatment of such infants places them at high risk for the development of congenital syphilis. Congenital syphilis developed in four of eight infants randomized to no treatment, and none of the 11 infants who received penicillin ($P = 0.04$) [245].

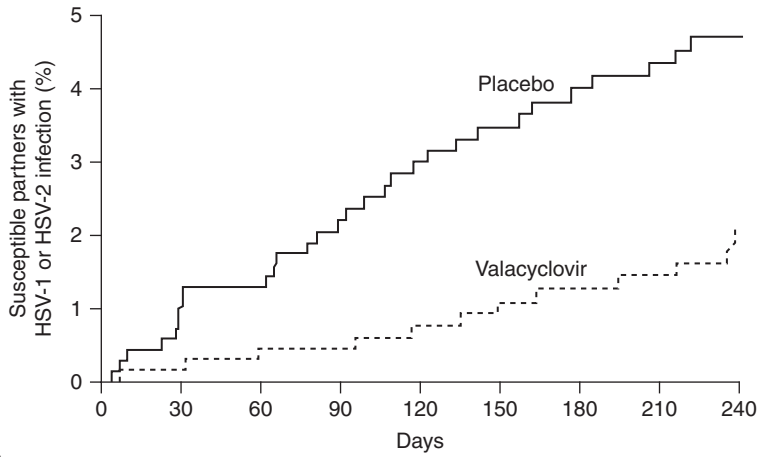
Treatment of genital herpes

Genital herpes may have a broad spectrum of clinical manifestations. First episodes of genital herpes may be primary (no previous infection with HSV-1 or HSV-2), or nonprimary, with primary episodes often being more severe [246–248]. Among individuals with primary genital herpes infection, intravenous acyclovir at a dose of 5 mg/kg every 8 hours was shown to be superior to placebo in time to healing of genital ulcers and in speed of elimination of viral shedding [249]. Subsequently, oral acylovir at a dose of 200 mg five times per day was shown to be superior to placebo in individuals with first episodes of genital herpes, both primary and nonprimary [250,251]. Further increasing the dose of antiviral drug does not result in improved outcomes; a randomized trial comparing a total of 4 g of acyclovir per day with 1 g per day found no differences between treatment groups [252].

Treatment of recurrent genital herpes episodes with oral acyclovir at doses of 200 mg five times a day or 800 mg twice a day has been shown to be superior to placebo in the elimination of symptoms and viral shedding [253–255]. The related drugs famciclovir (125 mg orally twice a day) and valacyclovir (500 mg orally twice a day), are superior to placebo [256,257], and equivalent to acyclovir in efficacy [258,259]. Because many individuals with recurrent genital herpes recognize prodromal symptoms such as itching or tingling prior to experiencing an outbreak, patient-initiated therapy on the basis of such symptoms is often advocated, and appears effective in reducing outbreak duration and in aborting outbreaks [256,257,259]. More recently, evidence has emerged that traditional 5-day courses of therapy with antiviral drugs can be shortened. A 3-day course of valacyclovir appears equivalent in efficacy to a 5-day course [260], while a 2-day course of oral acyclovir (800 mg three times per day) is superior to placebo in the reduction of duration of lesions and viral shedding [261].

Individuals who experience frequent recurrences may prefer to use suppressive chronic therapy with antiviral drugs. The use of acyclovir at a dose of 400 mg twice a day is superior to placebo [262–264], and to lower doses of acyclovir [265], in the reduction of outbreak frequency. Treatment with daily acyclovir for as long as 6 years appears to be safe and well tolerated by patients, and the emergence of viral resistance does not appear to be a problem in immunocompetent hosts [266–268]. Famciclovir (125 or 250 mg orally twice daily) and valacyclovir (250 mg twice daily, 500 mg once daily, or 1 g once daily) are also superior to placebo for the prevention of recurrences [267,269–271]. A recent metaanalysis of 14 placebo-controlled randomized controlled trials of suppressive therapy with acyclovir, famciclovir, or valacyclovir for the prevention of genital herpes outbreaks showed a pooled relative risk of developing at least one outbreak during therapy of 0.53 (95% CI 51–55) [272]. Subgroup analyses showed a clear dose–response relationship for famciclovir between total daily doses of 250 and 750 mg. Two short-term randomized controlled clinical trials comparing famciclovir 250 mg orally twice daily to valacyclovir 500 mg orally once daily demonstrated a similar time to first clinical recurrence (HR 1.17, 95% CI 0.78–1.76) but a shorter time to first virologically confirmed recurrence (HR 2.15, 95% CI 1.00–4.60) and high rate of HSV shedding (RR 2.33, 95% CI 1.18–4.89) with famciclovir [273].

Suppressive antiviral therapy appears to markedly reduce the frequency of asymptomatic viral shedding between recurrences as well [274]. To determine whether suppressive antiviral therapy could therefore decrease transmission of genital herpes, the Valacyclovir HSV Transmission Study randomized the HSV-2 seropositive partner in 1484 heterosexual, monogamous, HSV-2 serodiscordant couples to valacyclovir 500 mg orally daily versus matching placebo. This trial showed a significant reduction in both symptomatic (HR 0.25, 95% CI 0.08–0.75) and serologically confirmed (HR 0.52, 95% CI 0.27–0.99) HSV-2 infections among susceptible partners (Fig. 10.3) [275]. There was no difference between transmitters and nontransmitters in frequency of symptomatic reactivations in either the valacyclovir or the placebo arm of this trial, underlining the importance of asymptomatic



No. at Risk									
Placebo	741	689	663	627	604	581	562	546	387
Valacyclovir	743	693	667	647	623	599	589	572	388

Figure 10.3 Kaplan-Meier curve depicting time to transmission of HSV-1 or HSV-2 from an infected individual to an uninfected sex partner, based on the use of suppressive valacyclovir (500 mg orally 4 times daily) or placebo in the infected individual. Valacyclovir suppression reduces the risk of HSV transmission by approximately 50% (HR 0.45, 95% CI 0.24–0.84). Similar effects were seen in prevention of symptomatic HSV-2 infection in the initially uninfected partner. Reproduced from reference [275]: Corey L, Wald A, Patel R, et al. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. N Engl J Med 2004;350:11–20 © 2004 Massachusetts Medical Society. All rights reserved.

viral shedding in determining risk of HSV-2 transmission [276]. Suppressive antiviral therapy in individuals with frequent recurrences does appear to significantly improve health-related quality of life, and also reduces anxiety and depression scores on standardized instruments [277,278].

The epidemiology of maternal–fetal HSV transmission is complex. Available epidemiologic evidence from a large cohort of women in Washington State suggests that the highest risk of maternal–fetal HSV transmission occurs with maternal acquisition of genital HSV infection in the third trimester of pregnancy (adjusted OR 59.3, 95% CI 6.7–525) [25,279]. No randomized controlled trials exist to support the recommendation that women undergo cesarean section if herpetic lesions are present at the time of delivery [280]. However, among women in the Washington cohort with detectable HSV at delivery, a trend towards reduced transmission was seen in those who underwent cesarean delivery (adjusted OR 0.14, 95% CI 0.02–1.26). This is consistent with population-level data from California between 1995 and 2003, which identified a stable incidence of neonatal herpes over that time period in conjunction with an increase in the rate of genital herpes complicating labor and a concomitant increase in cesarean section due to herpes [281]. Randomized controlled trials have found that suppressive antiviral drugs in pregnancy reduce the risk of cesarean section, by reducing the likelihood that active herpetic lesions are present at delivery [282–284] (pooled RR of cesarean section 0.49, 95% CI 0.33–0.74). However, the question of whether antiviral drugs in pregnancy can actually reduce peripartum HSV transmission remains unresolved.

Treatment of chancroid

A variety of drug regimens have proven efficacious in the treatment of chancroid in randomized controlled trials. However, the development of drug resistance in *H. ducreyi* has made some treatment options obsolete in certain geographic areas. Traditional agents of choice for the treatment of chancroid included tetracyclines and sulfonamides, but resistance to these agents is now extremely common, and macrolides, fluoroquinolones, and third-generation cephalosporins are now preferred for the treatment of chancroid [285–290]. The results of randomized controlled trials evaluating the efficacy of these agents are presented in Table 10.7.

Of note, single-dose therapies with ciprofloxacin (500 mg) or azithromycin (1 g) have been proven equivalent to multiple-dose antibiotic regimens, while ceftriaxone (250 mg intramuscularly) appears equivalent to single-dose azithromycin [88,291–293].

Other antibiotic classes, including penicillins and aminoglycosides, may be useful in the treatment of chancroid. Although resistance to ampicillin by *H. ducreyi* is well described, resistance is mediated by β-lactamase production, and chancroid can be effectively treated with the addition of a β-lactamase inhibitor [294]. A single 2 g dose of spectinomycin is a useful alternative. A trial comparing spectinomycin to trimethoprim-sulfamethoxazole in Thailand found spectinomycin to be more likely to result in cure (RR of cure with spectinomycin 2.0, 95% CI 1.7–2.0) [295]. However, a randomized trial comparing erythromycin (500 mg orally three times a day for 5 days) to a single 2 g dose of spectinomycin found higher rates of cure with erythromycin (RR of cure with spectinomycin 0.9, 95% CI 0.8–1.0) [296].

Chancroid may be complicated by the development of fluctuant inguinal buboes. A small randomized trial compared aspiration to incision and drainage for the management of buboes during an outbreak of chancroid in New Orleans. Both forms of management appeared to be efficacious and acceptable, although six of 15 individuals who underwent aspiration experienced reaccumulation of purulent material, and required reaspiration ($P = 0.05$) [297].

Treatment of genital warts

A number of treatment modalities are available for the management of genital warts. These include topical agents, cryotherapy, surgical modalities (including scissors excision, laser ablation, and electrocautery), and interferon. While it is often suggested that genital warts involute spontaneously over time, it has been pointed out that there is little evidence to support this contention [298,299]. Important clinical outcomes in the study of genital wart treatment include reductions in wart area and rates of relapse, as well as rates of wart clearance.

Podophyllotoxin and imiquimod are both patient-applied topical therapies that have been proven efficacious in the treatment of genital warts in randomized, placebo-controlled trials (Table 10.8). A randomized trial comparing thrice-weekly application of 5% imiquimod cream with more frequent applications

Table 10.7 Randomized controlled trials evaluating macrolides, fluoroquinolones, and third-generation cephalosporins for the treatment of chancroid

Study population	Treatment arms	Primary outcome measure	Results	Comments	Reference
245 men and women attending an urban STD clinic in Nairobi, Kenya with genital ulcer disease compatible with chancroid	Single 500 mg dose of ciprofloxacin vs erythromycin 500 mg tid for 7 days	Ulcer healing or improvement among individuals proven to have chancroid by culture or PCR	No difference between treatment arms in healing or improvement (RR of cure with ciprofloxacin 1.0, 95% CI 0.8–1.2)	Double-blind, placebo-controlled	[88]
46 Indian men with clinical diagnosis of chancroid presenting to an outpatient specialty clinic	Ciprofloxacin 500 mg bid for 3 days vs erythromycin 500 mg qid for 7 days vs trimethoprim-sulfamethoxazole 160/800 mg bid for 7 days	Complete healing of ulcer 21 days after initial presentation	Cure in 29 of 31 individuals randomized to either erythromycin or ciprofloxacin. Relative risk of failure with trimethoprim-sulfamethoxazole 1.7, 95% CI 1.1–2.8	Open label trial. *H ducreyi* isolates resistant to trimethoprim-sulfamethoxazole. Individuals who failed initial therapy cured with ciprofloxacin or erythromycin	[289]
98 HIV-seronegative men presenting to a Nairobi clinic with culture-positive chancroid and negative syphilis evaluation	Single 400 mg oral dose of fleroxacin or trimethoprim-sulfamethoxazole 160/800 mg bid for 3 days	Clinical cure, defined as complete re-epithelialization at 1–2 weeks	Trend towards improved outcome with fleroxacin (RR of cure with fleroxacin 1.4, 95% CI 0.9–2.3)	Study performed as trimethoprim-sulfamethoxazole resistance being recognized in East Africa	[290]
204 men presenting to a Nairobi clinic with purulent genital ulcers	Azithromycin 1 gram orally vs erythromycin 500 mg qid for 7 days	Complete cure, defined as re-epithelialization of the ulcer base, ⩽21 days after initial treatment	No differences between treatment regimens in outcome (cure in 73/82 with azithromycin and 41/45 with erythromycin	HIV seropositivity associated with increased risk of failed therapy (OR 4.5, 95% CI 1.4–14.7)	[291]
139 men presenting to a Nairobi clinic with culture-positive chancroid and negative syphilis evaluation	500 mg ciprofloxacin as a single dose vs 500 mg ciprofloxacin or trimethoprim-sulfamethoxazole 160/800 mg bid for 3 days	Complete cure, defined as re-epithelialization of the ulcer base, ⩽21 days after initial treatment, and resolution of buboes	No differences between treatment regimens (cure seen in 28/46 with trimethoprim-sulfamethoxazole, 28/46 with single-dose ciprofloxacin, and 27/43 with 3-day ciprofloxacin regimen	Double-blind, placebo-controlled	[292]
197 men and women presenting to clinics in 4 US cities with genital ulcer but without evidence for syphilis	Single 1 g oral dose of azithromycin vs 250 mg ceftriaxone given intramuscularly	Complete healing of ulcer ⩾18 days after treatment in individuals with culture-proven chancroid	High rates of cure in both groups (32/32 with azithromycin, 29/33 with ceftriaxone), but azithromycin more efficacious (RR of cure 1.1, 95% CI 1.0–1.3)	High rates of healing among individuals with ulcers of uncertain etiology in both arms	[293]
48 men presenting to a Nairobi clinic with negative syphilis evaluation	Cefotaxime (1 g intramuscularly) with 1 g of probenecid orally, single treatment vs once-daily treatment for 3 days	Complete healing of ulcer at 28 days of follow-up	Total dose of 3 g cefotaxime superior to 1 g (RR of healing 1.4, 95% CI 1.0–2.0 with 3 g dose)	Double-blind, placebo-controlled	[391]

Table 10.8 Randomized placebo-controlled trials of selected therapeutic modalities for the treatment of genital warts

Study population	Intervention	Results	Reference
Podophyllotoxin			
60 men with a clinical diagnosis of genital warts attending government-affiliated clinics in Punjab region of Pakistan	Subjects randomized to treatment with podophyllotoxin 0.5% cream, interferon-alpha cream, or placebo up to 9 times per week for up to 4 weeks	Podophllotoxin cured more individuals at 4 weeks than placebo (RR of cure 3.0, 95% CI 1.2–7.7), but less efficacious than interferon-alpha (RR of cure 0.7, 95% CI 0.5–1.0)	[308]
60 men with a clinical diagnosis of genital warts attending government-affiliated clinics in Punjab region of Pakistan	Subjects randomized to treatment with podophyllotoxin 0.5% cream, interferon-alpha cream, or placebo up to 9 times per week for up to 4 weeks	Podophllotoxin cured more individuals at 4 weeks than placebo (RR of cure 3.7, 95% CI 1.2–11.2), but less efficacious than interferon-alpha (RR of cure 0.6, 95% CI 0.4–0.9)	[309]
57 men and women at several US centers, with prior complete resolution of genital warts	Participants randomized to receive 0.5% podophyllotoxin or placebo once daily, 3 days per week, for 8 weeks	Reduction in recurrence with podophyllotoxin 8 weeks after enrollment (RR of recurrence 0.4, 95% CI 0.1–1.0)	[392]
57 Swedish men with previously untreated genital warts	Subjects randomly assigned to receive up to 2 courses of 0.25% or 0.5% podophyllotoxin, or placebo, twice daily for 3 days	No resolution seen in placebo arm. Warts cleared after 2 cycles of treatment in 13/18 patients receiving 0.25% and 13/16 patients receiving 0.5% podophyllotoxin	[393]
109 men with at several US centers, with a clinical diagnosis of genital warts	Subjects randomly assigned to 0.5% podophyllotoxin or placebo for 3 consecutive days, followed by 4 days without treatment. Applications repeated for 2–4 weeks	25/56 podophyllotoxin treated men wart-free at some point during study; no individual was wart-free in placebo arm. Reduction in total wart area also seen with podophyllotoxin	[394]
72 women with a clinical diagnosis of exophytic vulvar condyloma	Subjects randomly assigned to 0.5% podopyllotoxin in either alcohol or cream formulation or placebo, 2 applications per day, 3 consecutive days per week, for up to 4 weeks	Trend towards greater efficacy with podophyllotoxin at 10 weeks (RR for clearance 2.1, 95% CI 0.9–4.7)	[395]
38 men with genital warts in Seattle, Washington	Subjects randomly assigned to 0.5% podophyllotoxin or placebo applied 3 consecutive days per week for up to 4 weeks	11/19 podophyllotoxin treated men wart-free at some point during study; no individual was wart-free in placebo arm. Reduction in total wart area also seen with podophyllotoxin	[396]
Imiquimod			
311 men and women with anogenital warts at multiple US centers	Subjects randomized to 5% or 1% imiquimod cream or placebo, 3 applications per week for up to 16 weeks	Higher rates of clearance of warts seen with 5% imiquimod (RR of clearance 4.5, 95% CI 2.5–8.1) and 1% imiquimod than with placebo. 5% imiquimod more efficacious than 1% imiquimod (RR of clearance 2.4, 95% CI 1.6–3.7)	[397]

Continued

Study population	Intervention	Results	Reference
279 men and women with 2 or more biopsy-proven external genital warts at multiple centers in the US	Subjects randomized to daily application of 5% or 1% imiquimod cream or placebo, for up to 16 weeks	Higher rates of clearance of warts seen with 5% imiquimod (RR of clearance 16.3, 95% CI 5.3–51.1) and 1% imiquimod than with placebo. 5% imiquimod more efficacious than 1% imiquimod (RR of clearance 3.6, 95% CI 2.1–6.2)	[398]
60 women with genital warts in Punjab region of Pakistan	Subjects randomly assigned to 2% imiquimod or placebo, up to 10 applications per week for 6 weeks	Higher rates of clearance seen with 2% imiquimod than placebo after 6 weeks (RR of clearance 25, 95% CI 3.6–172.6)	[399]
60 men with genital warts attending public health centers and municipal dispensaries in Punjab region of Pakistan	Subjects randomized to 2% imiquimod cream or placebo, 3 applications weekly for 4 weeks	Higher rates of clearance seen with 2% imiquimod (RR of clearance 7.0, 95% CI 2.3–21.0)	[400]
Intralesional interferon			
296 men and women with a clinical diagnosis of genital warts attending multiple centers in the US	Subjects randomized to 3 weekly intralesional injections of interferon alpha-2b or placebo, into up to 3 warts per subject, for 3 weeks	Higher rates of clearance of treated warts with interferon than with placebo at 16 weeks (RR for clearance of treated lesions 2.5, 95% CI 1.5–4.1). Higher percentage of interferon-treated subjects had a 50% or greater reduction in total wart area ($P < 0.001$)	[401]
158 men and women with a clinical diagnosis of at least 2 genital warts, covering at least10 mm^2 in area, treated at 4 US centers	Warts injected with interferon alpha or placebo twice weekly for up to eight weeks, or until disappearance of warts	Interferon alpha more efficacious than placebo three months after last injection (RR of clearance with interferon 2.9, 95% CI 1.8–4.8)	[402]
76 men and women from multiple US centers, with genital warts present despite the use of conventional therapy	A single wart from each patient was injected 3 times per week for 4 weeks with one of 3 interferon preparations or placebo	Significant difference between interferon preparations and placebo in resolution of injected warts over 16-week follow-up period ($P = 0.02$). No difference in efficacy between interferon preparations. Interferon did not affect noninjected warts	[403]
114 men and women with genital warts treated at six centers in the US	Single wart injected intralesionally with high dose interferon alpha, low dose interferon alpha, or placebo, 3 times weekly for 3 weeks	Both high dose interferon alpha more efficacious than low dose interferon alpha (RR of clearance 2.8, 95% CI 1.3–6.3), and placebo (RR of clearance 3.8, 95% CI 1.5–10.2) at 12 weeks. Low dose interferon alpha no better than placebo (RR of clearance 1.4, 95% CI 0.4–4.3)	[404]
41 women and 1 man aged 16 to 65 treated at a clinic in North Carolina	6 to 9 injections of interferon alpha-2b or placebo over a period of up to 29 days	Trend towards greater efficacy with interferon than placebo after 1 month (RR of clearance 3.0, 95% CI 0.9–10.0)	[405]

found no benefit with more frequent applications, and identified an increase in the incidence of adverse events [300].

Cryotherapy is commonly used for the treatment of genital warts, but has not been evaluated in placebo-controlled trials. This modality was superior to podophyllin in a randomized trial (RR of clearance 3.2; 95% CI 1.7–6.1), although this trial had high rates of loss to follow-up [301]. More prolonged application of liquid nitrogen (~10 s) increased the probability of wart clearance, but was associated with an increased risk of pain during treatment in a randomized trial (RR of clearance 1.7, 95% CI 1.2–2.4; RR of pain 2.3, 95% CI 1.4–3.9) [302].

Two randomized trials have compared the efficacy of cryotherapy to trichloroacetic acid (TCAA), with no significant difference seen in rates of clearance (pooled RR for wart clearance with cryotherapy 1.0, 95% CI 0.7–1.4) [303,304]. However, cryotherapy may also be less likely to cause genital ulceration than TCAA (OR of ulceration with cryotherapy 0, 95% CI 0–0.3) [304].

No placebo-controlled trials of surgical modalities for genital wart treatment have been performed to date. Randomized trials comparing laser surgery with conventional scissors excision, and electrocautery with cryotherapy, have failed to find any difference between modalities in terms of efficacy [305,306]. However, scissors excision of perianal warts was superior to podophyllin application both in initial wart clearance and in subsequent recurrence rates (RR of recurrence after scissors excision 0.3, 95% CI 0.2–0.7) [307].

Topical, intralesional and systemic interferon preparations have been evaluated for the treatment of genital warts. Both topical and intralesional interferon are more efficacious than placebo in the eradication of genital warts (Table 10.8). Topical interferon-alpha was more efficacious than podophyllotoxin in two randomized trials (pooled RR of clearance with interferon-alpha 1.6, 95% CI 1.2–2.1) [308,309]. A randomized trial comparing podophyllin plus intralesional interferon-alpha to podophyllin alone found a higher rate of wart clearance with interferon, but a high rate of relapse was seen in both treatment groups, and intralesional interferon was associated with adverse effects including fever, myalgia, gastrointestinal distress, and headache [310]. Although systemic interferons have been more efficacious than placebo in the clearance of genital warts, the addition of systemic interferon to such standard therapies as cryotherapy or podophyllin has been no more efficacious than standard therapies alone [311–316]. Further, the expense and potential toxicity of systemic interferon limits its practical value in most clinical situations.

Treatment of genital warts in immunocompromised individuals, including those with HIV infection, may be particularly challenging. A randomized trial comparing imiquimod 5% to placebo in individuals with HIV infection and CD4+ T-lymphocyte counts <100 cells/mL found no difference between the two arms in rates of wart clearance [317]. Cidofovir 1% gel may be a useful therapeutic option in HIV-infected individuals; a small randomized trial found higher rates of clearance with cidofovir (9/19 individuals) than with placebo (0/9 individuals, $P = 0.006$). A second randomized trial found the combination of cidofovir 1% gel and scissors excision to be more efficacious than either scissors excision or cidofovir gel alone in a population of individuals with HIV infection [318].

Patient factors other than immunocompromise may influence clearance of genital warts. An observational study carried out on individuals with genital warts in Leeds, UK, found increasing wart numbers associated with decreased clearance in response to therapy (hazard ratio for every 2-fold increase in wart numbers 0.70, 95% CI 0.45–0.86). Smoking was evaluated as a possible predictor of persistence in this study, and was not found to be predictive of wart persistence [319].

Treatment of trichomoniasis

Metronidazole appears to be a highly effective agent for the treatment of vaginal trichomoniasis. Double-blind randomized controlled trials have found no significant difference in efficacy between a single 2 g dose of metronidazole and 5- to 7-day courses of the drug dosed at 750–800 mg per day. Both regimens appear to result in parasitologic cure in over 85% of individuals [320,321]. Single-dose metronidazole for the treatment of trichomoniasis appears less efficacious if the drug is given as a single 1 g dose, although a single 1.5 g dose may be equivalent to a 2 g dose [297,298]. A single 2 g dose of tinidazole is equivalent in efficacy to 2 g of metronidazole for the treatment of vaginal trichomoniasis [322,323]. Tinidazole appears to be efficacious in individuals with prior failure of therapy associated with metronidazole-resistant trichomonads, and

eradicated infection in 22 of 24 women who had previously failed therapy with metronidazole for trichomonal vaginitis [324].

Topical therapies for trichomoniasis have been disappointing to date. A multicenter, open-label randomized trial comparing single-dose oral metronidazole to intravaginal clotrimazole or sulfanilamide-allantoin-aminacrine hydrochloride suppositories found metronidazole to be curative in 34/45 of subjects, while suppositories were associated with microbiologic failure in over 80% of participants [325]. Intravaginal 0.75% metronidazole gel was significantly less efficacious than oral metronidazole in a small randomized trial (RR of cure with gel 0.4, 95% CI 0.3–0.8) [326]. Topical nonoxynol-9 was ineffective in the treatment of vaginal trichomoniasis [327].

The association between asymptomatic carriage of *T. vaginalis* and preterm delivery led investigators to hypothesize that screening for and treating subclinical infections in pregnancy could reduce the risk of preterm delivery. However, in a randomized placebo-controlled trial, the incidence of preterm delivery was significantly higher in women treated with metronidazole than among those treated with placebo (RR 3.0, 95% CI 1.5–5.9). Screening for trichomoniasis in asymptomatic pregnant women cannot be recommended at this time [20].

Treatment of partners for prevention of reinfection

The importance of treating sex partners for the prevention of repeated infection has been demonstrated for several curable sexually transmitted infections, including trichomonal vaginitis, genital chlamydia, and gonorrheal infection in women. In a study in which partners of women with trichomoniasis were randomized to receive either tinidazole or placebo, reinfection was strongly associated with the receipt of placebo (RR 4.7, 95% CI 1.3–25.3) [328]. Additionally, analysis of data from a randomized controlled trial of a behavioral intervention in women with a baseline sexually transmitted infection found reinfection with gonorrhea or chlamydia to be strongly associated with sex with a partner who was not adequately treated (OR 5.6, 95% CI 3.0–10.5) [329].

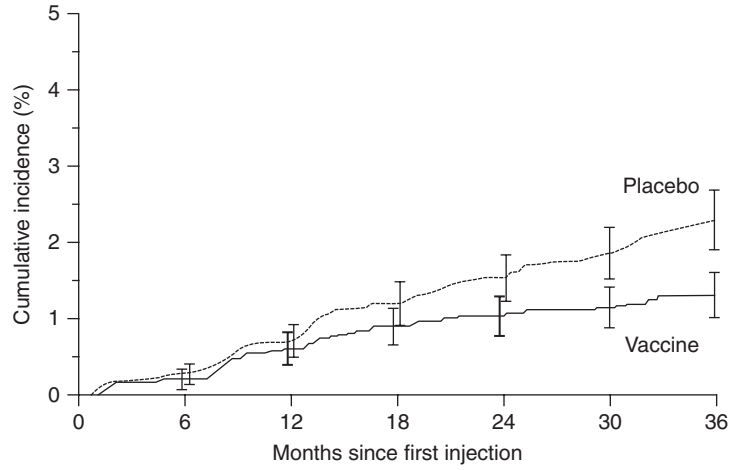
Patient delivery of medications to sex partners might help ensure partner treatment. Non-randomized studies have found lower rates of reinfection with chlamydia in women who delivered medications to their partners [330,331], and these findings have now been replicated in randomized controlled trials. A trial conducted in Seattle found that expedited delivery of therapy to sex partners reduced the risk of persistent or recurrent *Chlamydia* infection or gonorrhea in women and heterosexual men (RR for reinfection 0.75, 95% CI 0.57–0.97) [332]. A study restricted to men with urethritis found an even stronger protection against persistent infection with patient-delivered partner therapy (adjusted OR 0.38, 95% CI 0.19–0.74) [333]. A third trial restricted to women with *Chlamydia* cervicitis failed to find significant protection, but this may have been due to inadequate statistical power (OR of reinfection 0.80, 95% CI 0.62–1.05) [330].

Strategies for control of STI in the community

Vaccination

The past 5 years have witnessed a remarkable change in the extent to which vaccination is regarded as a mainstay of STI prevention strategies. While vaccination as a strategy for the prevention of bacterial STI has been unsuccessful to date, conjugate virus-like particle (VLP) vaccines against both oncogenic and wart-associated strains of human papillomaviruses (HPV 16 and 18, and HPV 6 and 11, respectively) are now in clinical use in many countries. In published randomized, placebo-controlled trials, these vaccines have been highly immunogenic (Fig. 10.4) [334–336], extremely effective at preventing acquisition of vaccine HPV strains by sexually active women [337–339], and have consistently been shown to reduce the risk of HPV-associated cervical dysplasia by >90% [338,340,341]. These vaccines are likely to reduce the risk of both future cervical cancer, and (not insignificantly) invasive follow-up testing for women with abnormal Papanicolau smears. Furthermore, in randomized trials, these vaccines prevent vulvar, vaginal, and perianal HPV-related lesions and neoplasia [342,343]. Unfortunately, effectiveness is limited to women without preexisting HPV infection [344], necessitating vaccination before or shortly after initiation of coitarche.

Although VLP HPV vaccines are associated with a risk of anaphylaxis higher than other conjugate vaccines, severe adverse events are rare (true anaphylaxis



No. at Risk							
Vaccine	6087	5918	5824	5733	5592	5427	2925
Placebo	6080	5942	5832	5736	5586	5420	2994
Cumulative No. of Subjects with an Endpoint							
Vaccine	0	13	36	53	61	67	76
Placebo	0	17	43	72	91	109	132

Figure 10.4 Effectiveness of a 4-valent virus-like particle human papillomavirus (HPV) vaccine against development of HPV-associated cervical intraepithelial neoplasia. In the intention-to-treat analysis depicted here, women were analyzed according to randomization, regardless of whether or not they had prevalent vaccine-strain HPV infection at the time of vaccination or whether they received vaccination. The overall risk reduction for cervical lesions associated with any HPV type was 20% (95% CI 8–31%) in the intention-to-treat analysis. Vaccination was also associated with a 34% (95% CI 15–49%) reduction in anogenital HPV lesions of any viral type in intention-to-treat analyses. Reproduced from reference [340]: Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007;356:1915–27, © 2007 Massachusetts Medical Society. All rights reserved.

occurs in approximate 2.6 per 100 000 vaccinations, 95% CI 1.0–5.3) [344]. Given the long latency of cervical cancer following HPV infection, data proving reductions in cervical cancer incidence as a result of vaccination, and trials of vaccine effectiveness in males, are still pending. However, a mathematical model synthesizing the best available data suggests that HPV vaccination is likely to be highly cost-effective relative to currently available health interventions; furthermore, cost-effectiveness would be enhanced by considering noncervical cancers prevented by these vaccines, and by modifying existing cervical screening regimens to account for the additional protection they provide[345].

A novel glycoprotein-conjugate vaccine may be efficacious for the prevention of genital herpes in women without prior serologic evidence of either HSV-1 or HSV-2 (RR 0.26, 95% CI 0.09–0.93), but has not been shown to be effective in men [346]. Effective vaccines are also available for hepatitis A and B virus infections, which may be sexually transmitted [347–351]. A single small randomized, placebo-controlled trial failed to identify protection associated with postexposure vaccination for sex partners of individuals with acute hepatitis B infection [352].

Population-based screening programs

Screening and use of curative or suppressive antibacterial and antiviral agents may provide an effective means of disrupting disease transmission, particularly if infections are asymptomatic or unrecognized in the absence of therapy. In nonpregnant populations, limited evidence exists to guide policy related to population-based screening for most pathogens. An exception is *C. trachomatis*, which is likely to be markedly underdiagnosed if testing is limited to those

with symptoms [353,354]. A randomized controlled trial of screening for genital chlamydia infection in women enrolled in a Washington State health maintenance organization found a significant reduction in the incidence of PID after 1 year of follow-up among screened women (RR 0.44, 95% CI 0.20–0.90) [355]. Screening for chlamydia has been suggested to be a cost-saving health intervention in high-prevalence populations [356], but a recent systematic review found numerous limitations in health economic evaluations of chlamydia screening [357]. Mathematical models that account for transmissibility do suggest that inclusion of males in screening programs is likely to provide additional gains in women's health at reasonable cost [358].

Mass antibiotic treatment in high-risk populations and outbreaks

Mass antibiotic treatment for STI has been proposed for outbreak control, prevention of HIV acquisition in high-risk populations, and for prevention of sequelae in pregnant women at increased risk of STI. Good evidence exists to support the use of such treatment in the latter population; in two randomized, placebo-controlled trials conducted in Kenya, the empiric administration of third-generation cephalosporins to women at 28–32 weeks of gestation found a reduced risk of stillbirth (pooled RR 0.54, 95% CI 0.36–0.81) and postpartum endometritis (pooled RR 0.50, 95% CI 0.31–0.81) [359,360]; and in a subgroup analysis restricted to pregnant women participating in the "Rakai study" (described below), empiric STI therapy was associated with a significant reduction in neonatal death (RR 0.83, 95% CI 0.71–0.97), as well as low birthweight, ophthalmia neonatorum, and maternal carriage of *T. vaginalis*, gonococcus, and *C. trachomatis* [361].

However, the primary endpoint in the Rakai study was prevention of HIV infection through treatment of non-HIV STI. This cluster-randomized controlled trial, in the Rakai district of Uganda, applied community-wide antibiotic treatment in an effort to slow HIV transmission. No impact was seen on HIV infection, but this trial did document significant reductions in syphilis (RR 0.8, 95% CI 0.7–0.9%) and trichomoniasis (RR 0.6, 95% CI 0.4–0.9%) in communities that received mass antibiotic therapy. Similar results were found in a randomized controlled trial of monthly azithromycin prophylaxis among HIV-seronegative female sex workers in Nairobi, Kenya: significant reductions in syphilis, gonorrhea and trichomoniaisis occurred without reduction in HIV risk [362]. The modest effect of these interventions and the potential impact of such a strategy on local antimicrobial susceptibility patterns argue against the use of such a strategy for primary control of STI other than HIV [179]. Indeed, other efforts to apply mass antibiotic therapy for reduction of STI risk have shown limited short-term effects, with rebound to baseline levels following discontinuation of mass therapy for gonorrhea [363], or in the case of mass antibiotic therapy for syphilis control, rebound in rates to levels higher than those seen prior to the intervention [364].

One possible reason for the failure of mass antibiotic treatment to reduce HIV infection in the Rakai study was suggested to be the high background prevalence of genital HSV-2 infection (which would not have been controlled by the antimicrobial agents administered) [365]. However, recent randomized trials that evaluated suppressive acyclovir therapy for HSV-2 seropositive African women [366,367], and men who have sex with men in the US and Peru [366], found no protective effect against HIV acquisition associated with anti-herpes therapy (pooled HR 1.14, 95% CI 0.86–1.51) [366,367].

Counseling and behavioral interventions

Several randomized controlled trials have evaluated behavioral interventions targeting groups perceived to be at increased risk of acquiring STI [368]. A recent systematic review identified marked between-study heterogeneity with respect to populations, interventions, and estimated effectiveness. However, behavioral and counseling interventions that are more extensive (e.g., multiple sessions, incorporate multiple modalities) do appear to have a moderate effect in reducing STI risk in adults and adolescents, with no increase in sexual risk-taking noted as a result of counseling [368]. For example, in one multicenter trial (Project RESPECT) conducted in publicly funded clinics in five US cities, evaluated changes in behavior and incidence of infection in individuals receiving a brief didactic message, brief counseling, or extended counseling. Both brief and extended counseling reduced the risk of laboratory-confirmed sexually transmitted infection at 6 months (RR for brief intervention 0.7, 95% CI 0.6–0.9, RR for enhanced intervention 0.7; 95% CI

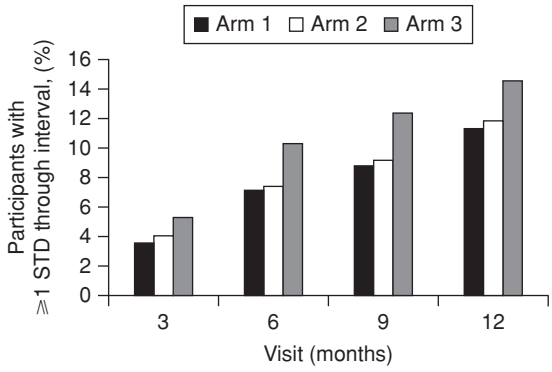


Figure 10.5 Effectiveness of clinic-based counseling interventions in the prevention of sexually transmitted infections. Clinic attendees enrolled in a multicenter trial were randomized to receive four interactive counseling sessions (Arm 1), two interactive counseling sessions (Arm 2), or didactic message on sexually transmitted infection risk-reduction (Arm 3). Reductions in sexually transmitted infection risk were seen with both counseling interventions, and persisted 12 months after initial counseling ($P = 0.008$). Reproduced from reference [369]: Kamb ML, et al. Efficacy of risk reduction counseling to prevent human immunodeficiency virus and sexually transmitted diseases: a randomized controlled trial. Project RESPECT Study Group. JAMA 1998;280(13):1165. Copyright © 1998, American Medical Association. All rights reserved.

0.5–0.9); a transient increase in condom use was also seen (Fig. 10.5). However, these effects diminished over time [369].

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CHAPTER 11
Human immunodeficiency virus

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Primary HIV infection

Case presentation 1

A 52-year-old homosexual man is feeling unwell with fever, malaise, a diffuse maculopapular rash and lymphadenopathy. He holidays regularly in Thailand and has had unprotected receptive anal sexual intercourse with a regular Thai partner as well as contact with five commercial sex workers in Bangkok. You suspect he has primary HIV infection and ask how best to make the diagnosis and whether he should be treated with antiretroviral drugs immediately.

Diagnostic confirmation

A study of 258 persons screened for primary HIV infection (PHI) compared the sensitivity and specificity of clinical symptoms, three HIV-1 RNA viral load assays, a p24 antigen enzyme immunoassay (EIA), and a third-generation enzyme immunoassay antibody test [1]. The symptoms most strongly associated with PHI in multivariate analysis were fever (odds ratio [OR] 5.2; 95% CI 2.3–11.7) and rash (OR 4.8; 95% CI 2.4–9.8). The sensitivity and specificity, respectively, for detecting pre-seroconversion HIV infection were: p24 antigen, 79% and 99%; third-generation EIA, 79% and 97%; HIV-1 RNA by branched chain DNA, 100% and 95%; HIV-1 RNA by polymerase chain reaction (PCR), 100% and 97%; HIV-1 RNA by transcription-mediated amplification testing, 100% and 98%. False-positive HIV-1 RNA tests were not reproducible and had values <3000 copies/mL, while only one person with confirmed PHI was in this range. PCR is still relatively expensive with longer turnaround times than enzyme-linked tests. Some fourth-generation antibody tests combine the detection of HIV antibodies with that of viral p24 antigen and can detect infection as early as 6 weeks post-exposure. Qualitative detection of HIV-1 RNA in saliva (when plasma levels are >4000 copies/mL) is now possible [2]. This test may be useful in diagnosing acute infection in adults as well as vertical infection in infants.

A number of rapid HIV antibody tests are available, sometimes referred to as "point-of-care" [3]. One of these is suitable for oral fluids [4]. Sensitivity and specificity were compared with results of the EIA and Western blot. OraQuick™ sensitivity was 99.7% with whole blood and 99.1% with oral fluid from 327 persons who were HIV-antibody positive by the conventional algorithm. Specificity was 99.9% with whole blood and 99.6% with oral fluid from 12 010 HIV-negative persons; EIA specificity was 99.7%. These results suggest that the oral fluid antibody test is comparable to EIA tests and useful as a convenient screening tool.

Early treatment

In PHI there are no data on long-term clinical outcomes. Any perceived benefit comes from *in vitro* studies showing better immunologic responses [5,6]. There is one randomized study from 1993 of zidovudine monotherapy versus placebo for 6 months in 77 patients with PHI [7]. There was no difference in the mean duration of the retroviral syndrome. Minor opportunistic infections (oral candidiasis, herpes zoster,

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and oral hairy leukoplakia) were less frequent in the zidovudine group (one infection) than in the placebo group (seven infections; $P = 0.009$ by the log-rank test). After adjustment for baseline CD4 cell count, the patients treated with zidovudine had an average gain of 8.9 CD4 cells/mm^3 per month (95% CI 1.4–19.1), whereas those receiving placebo had an average loss of 12.0 CD4 cells/mm^3 per month (95% CI 5.2–18.7), for a between-group difference of 20.9 CD4 cells/mm^3 per month (95% CI 8.5–33.2; $P < 0.001$). No long-term clinical benefits were found. The impact of short-term and longer-term treatment in PHI with highly active antiretroviral therapy (HAART) is currently being investigated by the international SPARTAC study.

Asymptomatic HIV infection

There is no good clinical evidence for when to start antiretroviral drug therapy in asymptomatic HIV-positive individuals. There is one Cochrane review (search date not stated, five randomized controlled trials [RCTs], 7722 people with asymptomatic HIV mainly with CD4 counts >200 cells/mm^3) comparing zidovudine given immediately versus zidovudine deferred until the early signs of AIDS [8]. It found that immediate versus deferred treatment significantly increased AIDS-free survival at 1 year (78/4431 [1.76%] with immediate zidovudine vs 131/3291 [3.98%] with deferred zidovudine; OR 0.52; 95% CI 0.39–0.68), but the difference was not significant at the end of the studies (median follow-up of 50 months; 1026/4431 [23.2%] with immediate zidovudine v 882/3291 [26.8%] with deferred zidovudine; OR 0.96; 95% CI 0.87–1.05). Overall survival was similar in the two groups at 1 year. The conclusion was that, although an initial effect was seen, this was not sustained. There is as yet no similar evidence for HAART. Results from treatment interruption studies (discussed later) have led some experts to recommend initiation of HAART at CD4 counts above 350 cells/mm^3, although there is at present no direct evidence on which to base this [9,10].

As far as harm from early zidovudine is concerned, in a metaanalysis of pooled toxicity data, early treatment in asymptomatic persons conferred a small but significant increase in the risk of anemia (relative risk [RR] of hemoglobin <8.0 g/dL, early vs deferred treatment 2.1; 95% CI 1.1–4.1; absolute risk [AR] 0.4 events per 100 person-years) [11]. There was also a small increase in risk of neutropenia with early treatment (AR 1.1 events per 100 person-years; $P = 0.07$).

Epidemiology of drug resistance, baseline genotyping, and response to HAART

The prevalence of mutations associated with drug resistance in treatment-naive patients differs among demographic regions and likely reflects access to antiretroviral therapy. In a multicenter US study, 14% of 371 isolates from treatment-naive patients had at least one resistance mutation [12]. A European study known as CATCH assessed resistance in over 1630 newly infected people between 1996 and 2002 [13]. Overall, primary resistance mutations were detected in 10%. A larger European study named SPREAD (Strategy to Control Spread of HIV Drug Resistance) gathered resistance and clinical data from 2008 newly infected and ART-naive HIV patients [14]. Thirteen percent had nucleoside reverse transcriptase inhibitor (NRTI) mutations at the start of follow-up period, but this decreased by half over time; the frequency of non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance mutations increased from 2.3% to 9.8%, and protease inhibitor (PI) resistance remained stable at 3–4%. An increase in resistance over time was also observed in non-B subtypes (from 2.0% in 1996–98 to 8.2% in 2000–01), reflecting increasing access to HAART in areas where non-B subtypes predominate. There have been recent data to suggest that the prevalence of resistance in the UK may be falling [15]. A peak in the number of individuals with transmitted drug resistance was observed in 2001–02, when one or more major resistance mutations were detected in 14% of all patients. By the end of 2004, however, only 8% of untreated individuals had resistance, a highly significant decline (P trend < 0.001). Among patients with recent infection, a similar pattern was detected, but the downward trend in the transmission of resistance occurred approximately 2 years earlier, from 2000 onwards (P trend $= 0.002$).

Transmission of drug-resistant virus

The clinical impact of acquiring a transmitted drug-resistant virus (TDR) in cohorts of seroconverters has been studied up to 1 year, and no significant difference was found between patients harboring TDR and those without on CD4 counts [16]. It is unclear whether unfit virus with a lower capacity to replicate will mean slower progression but the survey of 101

seroconverters found no evidence of a slower rate of disease progression, measured as time from estimated seroconversion date to a CD4 cell count of 350 cells/mm^3. Similar conclusions were reached in a 3-year follow-up of 46 Spanish seroconverters with available baseline genotypes [17]. However, San Francisco researchers have produced contradictory findings. They identified 130 seroconverters diagnosed since 1996, and found that those with genotypic evidence of drug resistance or virus with reduced replication capacity had significantly higher CD4 cell counts after controlling for duration of infection [18].

Transmitted primary resistance can persist for a long time. In the Spanish study, 10 patients with primary resistance mutations were followed over a median time of 41 months. In only one case was reversion to wild type observed after 7 years [17].

Transmitted resistance mutations can limit treatment options and reduce treatment response rates [19–23]. A retrospective study with 202 patients showed that, when initiating treatment without information on preexisting resistance, patients with preexisting mutations had a slower treatment response and a higher risk of treatment failure [20]. However, on careful consideration of any preexisting resistance, primary treatment success is often possible [24]. Most guidelines now recommend baseline genotyping in new patients to guide therapy [25,26] and it is considered to be cost-effective [27].

Transmission rates of resistant virus are possibly underestimated. Minority viral populations below 25% are not detected by standard sequencing techniques. Forty-nine virus isolates from acute seroconverters were tested for the presence of L90M, K103N, and M184V by quantitative realtime PCR using specific oligonucleotides for the three key resistance mutations [28]. In 10 out of 49 patients these mutants were detected. In 5 of these 10 patients the detected population represented a minor viral quasi-species and was not detected by direct sequencing.

Prognostic features for progression of disease

There is conflicting evidence about the value of viral load at baseline. Early studies suggested that high viral load was associated with an increased risk of death and it is associated with a more rapid fall in CD4 count [29]. However, an updated analysis of outcomes for people starting HAART showed only a small effect of viral load influencing outcome [30]. During 61 798 person-years of follow-up, there were 1303 AIDS events and 1005 deaths. The risk of disease progression at 1 to 5 years after beginning treatment was calculated according to five key baseline variables: CD4 count, viral load, age, transmission category, and CDC stage. Overall, a CD4 count <200 cells/mm^3, viral load > 5 log (100 000 copies/mL), age > 50, being an injecting drug user, and being in CDC stage 3 predicted a poorer outcome. (There is a useful online risk calculator at http://www.art-cohort-collaboration.org)

Summary

Nucleic acid-based tests are sensitive and specific for the diagnosis of primary HIV infection. Newer methods may be available for rapid "near patient" testing. There are no published RCTs evaluating delayed versus early treatment with HAART, although most guidelines now suggest treatment for symptomatic early disease and CD4 counts of 350 cells/mm^3 and higher [10,31]. RCTs conducted when zidovudine was the only drug available found no significant difference between immediate versus delayed treatment in survival at 1 year despite early changes in surrogate markers. The increase in transmitted drug resistance means that baseline genotyping is recommended to guide therapy.

Case presentation 1 (continued)

The patient tests positive for HIV antibody on multiple ELISA tests. His CD4 count is 560 cells/mm^3 with a HIV viral load of 100 000 copies/mL by PCR which is Clade E and found to be wild type. He is HBV, HCV, and VDRL negative. He is offered treatment because he is symptomatic but declines it. He has a calculated risk of AIDS after starting HAART of 7.4% (95% CI 6.3–8.6) and of death of 3.2% (95% CI 2.5–3.9) at the end of year 3 of treatment.

Tuberculosis

Case presentation 2

A 38-year-old female asylum seeker from Ethiopia is admitted directly from an airport health screening

continued

Case presentation 2 (continued)

clinic. She has an abnormal chest radiograph with a cough, hemoptysis, and weight loss. On examination she has a fever with a temperature of 38.2°C, a pulse of 80 per minute, blood pressure 142/80 mmHg, and respiratory rate of 24 per minute. She looks pale and has widespread lymphadenopathy and hepatosplenomegaly. Her full blood count shows a hemoglobin of 8.4 g/dL, white cell count of 4.3×10^9/L, platelets of 166×10^9/L. Blood film is normochromic and normocytic and there are no malarial parasites seen on three occasions. Biochemistry is normal. Her chest radiograph shows left apical infiltration. She tests seropositive for HIV-1 infection, hepatitis B surface and core antibody positive, but she is HBV-antigen negative. She is hepatitis C seronegative and VDRL negative. CD4 count is 310 cells/mm^3, viral load 70 000 copies/mL. You suspect she has *Mycobacterium tuberculosis* infection complicating HIV infection. She has evidence of previous hepatitis B infection. You question how best to confirm the diagnosis of tuberculosis (TB) and what your treatment options are.

The prevalence of *Mycobacterium tuberculosis*/HIV coinfection worldwide is 0.36% and 511 000 incident TB cases (9%) have HIV infection [32]. Of the estimated 33.2 million people currently living with HIV infection, 22.5 million of them are in Africa [33]. An estimated 1.84 million (1.59–2.22 million) people died of TB in 2000 of which 12% were attributable to HIV; in South Africa the attributable rate was 59%. The overall case fatality rate of HIV-infected TB cases has been estimated to be over 50%. Eighty percent of all incident TB cases have been found in 22 developing countries and nine of ten countries with the highest incidence rates per capita were in Africa.

Diagnosis

Significant clinical differences have been found between patients who are sputum-smear positive with acid-fast bacilli (AFB) and those who are smear negative with respect to cough, sputum production, and typical chest radiograph appearance (79%, 76%, and 79% sensitivity, respectively, for smear positive compared with 46%, 43%, and 40% for smear negative) [34]. In this study, there was no difference between HIV-positive and HIV-negative patients.

Sputum samples are just as likely to be AFB positive in HIV-positive as HIV-negative patients [35] and induced sputum may increase the yield [36]. Concentration methods of liquefied sputum in a large cohort of consecutive patients with suspected pulmonary TB showed that the overall sensitivity increased from 54.2% using conventional direct microscopy to 63.1% after concentration ($P = 0.015$) [37]. In HIV-positive patients, sensitivity increased from 38.5% to 50.0% ($P = 0.0034$).

Treatment

The efficacy of a 6-month short-course quadruple drug regimen of chemotherapy for pulmonary TB in the presence of HIV infection was confirmed in a study performed in Kinshasa, Zaire [38]. After 6 months, the rates of treatment failure between HIV-positive and HIV-negative participants were similar at 3.8% and 2.7%, respectively. At 24 months, the HIV-positive patients who received 6 months' extended treatment of rifampicin and isoniazid twice weekly had a relapse rate of 1.9%, as compared with 9% among the HIV-positive patients who received placebo for the second 6 months ($P = 0.01$). Extended treatment, however did not improve survival.

A prospective cohort study comparing a daily regimen of ethambutol, isoniazid, rifampicin, and pyrazinamide for 2 months, followed by ethambutol and isoniazid three times weekly for 6 months (2EHRZ/6E3H3); or the same initial intensive phase as the first regimen, followed by 4 months or 6 months of daily rifampicin and isoniazid (2EHRZ/4HR) and (2EHRZ/6HR) showed that the 2EHRZ/6E3H3 regimen was safe and effective but had a significant risk of relapse [39]. The relapse rate was 18.2 per 100 person-years observation (PYO) for the intermittent ethambutol arm compared to 9.7/100 PYO ($P = 0.0063$) and 4.8/100 PYO ($P = 0.0001$) in patients treated with 2 EHRZ/4HR or 2EHRZ/6HR, respectively.

A WHO-recommended 8-month regimen based on ethambutol and isoniazid was evaluated in a randomized clinical trial against a 6-month standard regimen in 1355 patients with newly diagnosed smear-positive pulmonary tuberculosis [40]. Subjects were assigned one of three regimens: daily ethambutol, isoniazid, rifampicin, and pyrazinamide for 2 months, followed by ethambutol and isoniazid for 6 months (2EHRZ/6HE); the same drugs but given

three times weekly in the initial intensive phase (2[EHRZ]3/6HE); or the same initial intensive phase as the first regimen, followed by 4 months of daily rifampicin and isoniazid (2EHRZ/4HR). At 2 months, a significantly higher proportion of patients assigned the daily intensive phase than of those assigned the three-times-weekly regimen were culture negative (700/828 [85%] vs 333/433 [77%], $P = 0.001$). At 12 months after the end of chemotherapy, the proportions of unfavorable outcomes were 36 of 346 (10%) with 2EHRZ/6HE, 48 of 351 (14%) with 2(EHRZ)3/6HE, and 17 of 347 (5%) with 2EHRZ/4HR. Both 8-month regimens were significantly inferior to the control 6-month standard regimen (difference between control and 2EHRZ/6HE 5.5%, 95% CI 1.6–9.4; between control and 2(EHRZ)3/6HE 8.8%, 95% CI 4.5–13.0). Adverse effects leading to interruption of treatment for 7 days or longer occurred in 28 patients (12 2EHRZ/6HE, five 2[EHRZ]3/6HE, 11 2EHRZ/4HR).

Antituberculosis prophylaxis

Without prophylaxis, people who are HIV-positive and tuberculin skin test-positive have a 50% or more lifetime risk of developing active TB compared with a 10% lifetime risk in people who are HIV-positive but tuberculin skin test-negative [41]. Two systematic reviews have found that anti-TB prophylaxis reduces the rate of developing active TB and death in the short term in people who are HIV-positive and tuberculin skin test-positive. A Cochrane review identified 11 well-conducted RCTs in 8130 HIV-positive adults from Haiti, Kenya, USA, Zambia, Spain, and Uganda [42]. All evaluated isoniazid (6–12 months) either compared with placebo or combination therapy (3 months). Mean follow-up was 2–3 years, and the main outcomes, stratified by tuberculin skin test positivity, were TB (either microbiologic or clinical) and death. Among tuberculin skin test-positive adults, anti-TB prophylaxis significantly reduced the incidence of TB (RR compared with placebo 0.38; 95% CI 0.25–0.57) and was associated with a trend towards reducing the risk of death (RR compared with placebo 0.80; 95% CI 0.63–1.02). Among tuberculin skin test-negative adults, there was no significant difference in risk of TB (RR compared with placebo 0.83; 95% CI 0.58–1.18) or death. There was a significant increase in adverse drug reactions requiring cessation of treatment on treatment compared with placebo (RR 2.49; 95% CI 1.64–3.77).

The second review of seven trials with 4529 people compared isoniazid with placebo or no treatment [43]. Among tuberculin skin test-positive participants the incidence of TB was significantly reduced (RR compared with placebo 0.40; 95% CI 0.24–0.65), but this was not so among tuberculin skin test-negative participants (RR compared with placebo 0.84; 95% CI 0.54–1.30). This review found no evidence of any impact on mortality. In this analysis, the estimated RR of stopping treatment because of adverse reactions was 1.36 (95% CI 1.00–1.86) [43].

A metaanalysis concluded that RZ is equivalent to INH in terms of efficacy and mortality in the treatment of latent tuberculosis infection. However, this regimen increases the risk of severe adverse effects compared with INH in non-HIV-infected persons [44].

There is insufficient evidence about the long-term effects of prophylaxis on rates of TB and death, and recent studies have found no evidence of benefit in people who are HIV-positive but tuberculin skin test-negative [45].

Summary

TB remains one of the commonest causes of illness in the world both in HIV-infected and uninfected individuals. The diagnostic and therapeutic approach should be the same. Anti-TB chemoprophylaxis may be useful in HIV-positive people who are also tuberculin skin test-positive. However, in areas with constantly high rates of TB exposure, the impact of this is not clear.

Case presentation 2 (continued)

Her sputum is positive for acid-fast bacilli and she is commenced on rifampicin, isoniazid, pyrazinamide, and ethambutol orally for 6 months. Sputum culture is positive for *Mycobacterium tuberculosis* which is sensitive to rifampicin, pyrazinamide, and ethambutol but resistant to isoniazid and streptomycin.

The main concern in this patient is to treat her TB infection effectively. She is at some risk of hepatotoxicity (see later). Since this patient's CD4 count is adequate it would be prudent not to commence any other

potentially hepatotoxic drugs or drugs that potentially may interact with her anti-TB therapy; starting HAART can probably be safely deferred. Careful consideration needs to be given to the risk of the patient having multidrug-resistant tuberculosis (MDR-TB). Previously in the UK the main risk was from people previously treated for TB, but nowadays travel is important. Twenty-nine papers were eligible for a metaanalysis [46]. The pooled risk of MDR-TB was 10.23 times higher in previously treated than in never-treated cases, with wide heterogeneity between studies. Study design and geographic area were associated with MDR-TB risk estimates in previously treated patients; the risk estimates were higher in cohort studies carried out in western Europe (RR 12.63; 95% CI 8.20–19.45) than in eastern Europe (RR 8.53; 95% CI 6.57–11.06). MDR-TB cases were more likely to be foreign born (OR 2.46; 95% CI 1.86–3.24), younger than 65 years (OR 2.53; 95% CI 1.74–4.83), male (OR 1.38; 95% CI 1.16–1.65), and HIV positive (OR 3.52; 95% CI 2.48–5.01).

Pneumocystis jiroveci (carinii) pneumonia

Case presentation 3

A 42-year-old Zimbabwean male nurse presents to the Accident and Emergency Department. He is short of breath on exertion and has a fever of 39°C, pulse 110 per minute, and a blood pressure of 110/76 mmHg. Pulse oximetry shows an oxygen saturation of 83% on room air. You suspect *Pneumocystis jiroveci* pneumonia (PCP) and wonder how best to investigate and manage him.

PCP remains the most common AIDS-related opportunistic infection (OI), usually occurring among those not receiving primary care [47].

Diagnosis

Kovacs et al. [48] described the differences between the clinical characteristics of PCP in 49 HIV-infected and in 39 HIV-negative persons. At presentation, patients with AIDS had a longer median duration of symptoms (28 vs 5 days) and higher median room air arterial oxygen tension (69 vs 52 mmHg, 9.2–6.9 kPa). In HIV-positive patients presenting with respiratory symptoms the sensitivity of induced sputum for the diagnosis of *P. carinii* was 13% and of BAL 77%. In the subgroup of patients with an adequate induced sputum sample, the sensitivity of induced sputum was 28% [49]. The sensitivities of different stains for detection of *P. carinii* in induced sputum were 92% with silver stain, 97% with direct immunofluorescent antibody (DFA), 97% with indirect immunofluorescent antibody (IFA), and 92% with Diff-Quik (DQ) (a modified Giemsa stain). The sensitivities for detection in bronchoalveolar lavage (BAL) were 86% with silver stain, 90% with DFA, 86% with IFA, and 81% with DQ [50]. PCR seems to be more sensitive than any of these methods [51] but newer molecular techniques are still not in routine clinical use [52,53].

Typical radiographic features of PCP are bilateral, symmetrical ground-glass opacities, but a wide variety of radiographic findings are observed. In 34 patients, high-resolution computed tomography of the lung showed ground-glass opacities sparing the lung periphery (41% of episodes) or displaying a mosaic pattern (29%), or being nearly homogeneous (24%), ground-glass opacities associated with air-space consolidation (21%), associated with cystic formation (21%), associated with linear-reticular opacities (18%), patchily and irregularly distributed (15%), associated with solitary or multiple nodules (9%), and associated with parenchymal cavity lesions (6%) [54].

Treatment

In the pre-AIDS era, co-trimoxazole (trimethoprim-sulfamethoxazole, TMP-SMX) was shown to be as effective as pentamidine in children with PCP and with fewer side effects [55]. In a study of PCP in HIV, 31 (86%) patients treated with co-trimoxazole and 20 (61%) with pentamidine survived and were without respiratory support at completion of treatment (95% CI for the difference in response, 5 to 45; $P = 0.03$) [56]. The arterial alveolar oxygen gradient ([A–a] DO_2) improved by greater than 1.3 kPa (10 mmHg) 8 days earlier for co-trimoxazole recipients (95% CI for the difference in response, -1 to 17; $P = 0.04$). Co-trimoxazole caused a rash (44%) and anemia (39%) more frequently ($P = 0.03$), whereas pentamidine caused nephrotoxicity (64%), hypotension (27%), or hypoglycemia (21%) more frequently ($P = 0.01$).

There is evidence from RCTs that corticosteroids are a useful adjunct to therapy in severe PCP. Six studies were

included in a metaanalysis [57]. Risk ratios for overall mortality for adjunctive corticosteroids were 0.54 (95% CI 0.38–0.79) at 1 month and 0.67 (95% CI 0.49–0.93) at 3–4 months of follow-up. Numbers needed to treat, to prevent one death, are nine patients in a setting without highly active antiretroviral therapy (HAART) available and 22 patients with HAART available. Only the three largest trials provided data on the need for mechanical ventilation with a risk ratio of 0.37 (95% CI 0.20–0.70) in favor of adjunctive corticosteroids.

In mild disease (O_2 saturations >90% by pulse oximetry), early deterioration developed in 7/12 patients on placebo and 1/11 patients taking 60 mg per day oral prednisolone respectively ($P = 0.027$). Even though patients suffering early deterioration in the placebo group were switched to corticosteroids, significant differences between the groups remained at day 30 with regard to exercise tolerance [58].

Alternative treatments

The combination of clindamycin plus primaquine appears to be the most effective alternative treatment for patients with PCP who are unresponsive to first-line therapy [59]. In a metaanalysis of 27 published clinical drug trials, case series, and case reports 497 patients with microbiologically confirmed PCP (456 with HIV), whose initial antipneumocystis treatment had failed and who required alternative drug therapy, were reviewed. Efficacies of salvage regimens were as follows: clindamycin-primaquine 42–44 (88–92%) of 48 patients, $P < 0.001$; atovaquone 4/5 (80%); eflornithine hydrochloride 40/70 (57%), $P = 0.01$; co-trimoxazole 27/51 (53%), $P = 0.08$; pentamidine 64/164 (39%); and trimetrexate 47/159 (30%).

Summary

PCP remains the most common AIDS-related OI and there is good evidence supporting the use of co-trimoxazole and, if severe, steroids for its treatment.

Case presentation 3 (continued)

PCP is suspected on CXR and confirmed on silver staining of BAL fluid and he recovers well with intravenous co-trimoxazole therapy and steroids. He is continued on oral co-trimoxazole as secondary prophylaxis.

Antiretroviral regimen selection and adherence

Case presentation 4

A 28-year-old homeless, intravenous drug user is admitted with widespread psoriasis to the dermatology ward. He is found to have diffuse generalized lymphadenopathy and oral candidiasis. He is tested for HIV and found to be positive. His CD4 count is 120 cells/mm^3 and the viral load is >500 000 copies/mL. He is hepatitis C antibody-positive, HCV RNA-positive and hepatitis B surface antigen-negative. He wants to know what treatment you would recommend and you consider what might be useful in helping him to adhere to the treatment plan.

Which drugs to start?

Current first-line ART combination strategies are the result of historic developments in antiviral therapy, with the NRTIs being the first class to show clinical benefits. Therapy with a single NRTI followed by dual NRTIs however resulted in viral, immunologic, and clinical failure due to viral resistance, but with the use of three agents from two classes a sharp decline in AIDS morbidity and mortality was observed [60].

Number of drugs in first-line regimen

The question of which drugs to start in the treatment of naive patients is still unanswered [10] and unlikely to be addressed in a large enough trial; however, a large systematic review has provided evidence that three drugs are better than two, and two are better than monotherapy [61]. There were 20 404 patients included in the 54 RCTs with 66 comparison groups included in the analysis. For both the clinical outcomes and surrogate markers, combinations with up to, and including, three drugs (HAART) were progressively and significantly more effective. The odds ratio for disease progression or death for triple therapy compared with double therapy was 0.6 (95% CI 0.5–0.8). There was heterogeneity in effect sizes probably related to the different drugs used and differences in trial design.

A Cochrane review has shown that in HIV-infected adults who have responded to an initial three- or four-drug regimen, a two-drug maintenance regimen

is associated with a higher risk of virologic failure compared with three or four drugs (OR 5.55; 95% CI 3.14–9.80) [62]. Other induction-maintenance regimens have been studied. The Forte trial compared induction with four drugs and maintenance with three drugs (two NRTIs, one NNRTI and one PI for 24 to 32 weeks, until viral load <50 copies/mL, followed by two NRTIs and one NNRTI compared with a standard dual NRTI and a single NNRTI regimen) [63]. More patients in the three-drug arm had virologic failure at 24 and 32 weeks. After 48 weeks, more patients in the induction/maintenance arm had viral loads below 50 copies/mL. There were no significant differences in the number of patients with serious adverse events or progression to AIDS or death between the two arms. In contrast, the TIME study did not provide support for a four-drug approach; patients were treated with AZT, 3TC, abacavir, and efavirenz for 48 weeks, then randomized to continue with the four-drug regimen or to drop efavirenz [64]. Despite low tolerability of the initial four-drug combination, intent-to-treat analysis revealed that the two approaches were equivalent at week 72. A similar approach was tested in the ESS40013 study, again with no significant differences in the proportions of patients with viral loads below 50 copies/mL and time to treatment failure between the two arms of the study 48 weeks after withdrawal of efavirenz from the maintenance arm [65].

Triple nucleoside vs dual nucleoside plus NNRTI

There are no data concerning which drugs have superior clinical outcomes. Recent studies looking at surrogate markers, in particular a drop in viral load to below a detectable level at 48 weeks seem to favor efavirenz-containing combinations. ACTG 5095 showed that efavirenz plus zidovudine-lamivudine with or without abacavir was virologically superior to the triple nucleoside combination of zidovudine-lamivudine-abacavir (Trizivir™) with 61% (95% CI 50–72%) having HIV-1 RNA <50 copies/mL at week 48 in the triple nucleoside group compared to 83% (95% CI 78–88%) in the combined efavirenz groups [66]. Triple nucleoside analogs alone are not recommended as standard therapy for this reason [10]. There was, however, no significant difference in CD4 count rise at the end of the follow-up period between groups.

Efavirenz vs nevirapine as NNRTI

Nevirapine may be as potent as efavirenz for up to 48 weeks. In a large international trial comparing these two NNRTIs 1216 antiretroviral-naive patients were randomized to receive nevirapine once daily, nevirapine twice daily, efavirenz, or a combination of efavirenz and nevirapine [67]. All patients took a background combination of lamivudine and stavudine. Viral suppression rates below the limit of detectability (<50 copies/mL) were as follows: 70.0% (95% CI 63.5–76.0) for nevirapine once daily, 65.4% (95% CI 60.4–70·1) for nevirapine twice daily, 70.0% (95% CI 65.2–74.5) for efavirenz, and 62.7% (95% CI 55.7–69.3) for nevirapine plus efavirenz. Overall, there were no significant differences in any of the four pairwise comparisons. These results, however relate to surrogate markers and not to clinical outcome; there was more hepatic toxicity in the nevirapine arms and adverse events were higher in the dual NNRTI arm.

NNRTI vs boosted PI as third agent

ACTG 5142 recruited 757 antiretroviral-naive people with a viral load >2000 copies/mL and any CD4 count (median 182 cells/mm^3) [68]. The open-label design randomized study participants to standard doses of efavirenz or lopinavir/ritonavir with lamivudine and a second NRTI, or to 533/133 mg of lopinavir/ritonavir twice daily plus standard-dose efavirenz. The primary endpoint was time to virologic failure; the median follow-up was 112 weeks. The time to virologic failure proved significantly faster in people who started lopinavir/ritonavir as the third agent rather than efavirenz ($P = 0.006$). However, people randomized to the boosted PI gained significantly more CD4 cells through 96 weeks than did people taking efavirenz.

The results of the 5-year FIRST trial CPCRA 058 that compared a PI plus NRTI versus NNRTI plus NRTI versus a three-class strategy support ACTG 5142 in finding a better virologic response to first-line NNRTIs than PIs [69]. However of the 1397 enrolled in FIRST, most randomized to NNRTI therapy took efavirenz, while 74% randomized to PIs used no ritonavir boost. The study found no difference between NNRTI and PI regimens in a composite endpoint including CD4 drop, progression to AIDS, and death (NNRTI versus PI hazard ratios [HRs] for the composite endpoint were 1.02 (95% CI

0.79–1.31), 1.07 (0.80–1.41), 0.95 (0.66–1.37), and 0.66 (0.56–0.78), respectively). 1196 patients were assessed for the three-class versus combined two-class primary endpoint. Mean change in CD4 cell count at or after 32 months was +234 cells/mm^3 and +227 cells/mm^3 for the three-class and the combined two-class strategies ($P = 0.62$), respectively. HRs (three-class vs combined two-class) for AIDS or death and virologic failure were 1.15 (0.91–1.45) and 0.87 (0.75–1.00), respectively. Better outcomes with an NNRTI compared with a PI may well be a class effect as similar findings were observed when ritonavir-boosted amprenavir was used as the PI [70].

Choice of NRTI

A large number of studies have been conducted to compare different NRTIs in combination with an NNRTI. None have shown differences in clinical endpoints, although 48-week virologic suppression rates have often favored newer agents such as abacavir and tenofovir. These differences are thought to be related to better tolerability/toxicity profiles rather than antiviral potency. Guidelines in well-resourced settings now recommend against stavudine and didanosine due to long-term toxicity concerns [10].

Side effects and drug–drug interactions associated with HAART

Aside from virologic and immunologic efficacy, there are other considerations when selecting combinations for individual patients. For example, the teratogenicity of efavirenz in animal studies makes it less attractive for women of childbearing age although recent data do not support substituting another drug for efavirenz in pregnancy [71]. Zidovudine is usually avoided in patients with anemia or when anemia can be predicted to occur with treatment such as with ribavirin for HCV [72] or chemotherapy for lymphoma. Nevirapine is more likely to cause severe rashes in women rather than men [73] and is also more likely to cause symptomatic liver function test derangement than efavirenz in women with CD4 counts above 250 cells/mm^3 and in men with CD4 counts above 400 cells/mm^3 [74]. Importantly, drug-drug interactions between rifampicin as part of antituberculosis therapy and nevirapine (a potent hepatic enzyme inducer) and boosted protease inhibitors are also key considerations in selecting regimens for TB/HIV-coinfected patients.

There are complex interactions between antiretroviral drugs and with other drugs. The website http://www.hiv-druginteractions.org/is a useful resource.

Pharmacogenomic screening for HLA-B*5701 is now being recommended, especially in white populations. In a double-blind, prospective randomized study of 1956 patients who had not previously received abacavir, the risk of an abacavir hypersensitivity reaction was reduced in patients who had prospective HLA-B*5701 screening (immunologically confirmed hypersensitivity reaction 0% vs 2.7% in the control group, $P < 0.001$) [75]. As well there was a significantly lower incidence of clinically diagnosed hypersensitivity reaction in the prospectively screened group (3.4%) than in the control group (7.8%) ($P < 0.001$).

The World Health Organization's HIV treatment guidelines panel (http://www.who.int/hiv/art/ARTadultsaddendum.pdf) has concluded that the recommended adult dose of stavudine (d4T) should be reduced to 30 mg twice daily for adults weighing more than 60 kg, following a review of a metaanalysis of previously unpublished clinical trials. The analysis shows that a 30 mg dose is just as effective as a 40 mg dose, but carries less risk of side effects such as peripheral neuropathy [76].

Compliance/adherence

Compliance has been shown to be an important factor in the long-term outcome of treatment. It may be that the easiest drug combination to comply with will be the most effective irrespective of drug potency or resistance profile. Adherence to any long-term drug regimen is difficult; however, it is of particular importance in the treatment of HIV because of the propensity of the virus to mutate and escape drug control. Good adherence can predict for viral suppression [77] and the development of viral resistance is associated with low blood drug levels that are usually because of poor adherence [78,79]. Even a 10% increase in adherence can lead to a 20% reduction in disease progression [80]. After controlling for potential confounding variables, patients who were less than 95% adherent to medications were 3.5 times more likely to have treatment failure (HIV-1 RNA >50 copies/mL) than subjects with adherence rates of 95–100%. The strongest predictor of adherence was adverse clinical events (e.g., dermatologic, gastrointestinal

symptoms): patients with adverse events were 12.8 times less likely to have 95–100% adherence [81].

To assess the effect of HAART adherence on survival in HIV-infected patients, a cohort study was performed on 1219 patients who began ART during the period 1990–99. In multivariate analysis, the variables that presented significant differences with respect to mortality were clinical stage at the beginning of treatment (AIDS: relative hazard [RH] = 2.97; 95% CI 2.14–4.13), CD4 cell count (<200 cells/mm^3: RH = 5.89; 95% CI 3.44–10.10), type of treatment (monotherapy: RH = 9.76; 95% CI 4.56–20.9); two drugs (RH = 9.12; 95% CI 4.23–19.64), and adherence (nonadherence: RH = 3.87; 95% CI 1.77–8.46) [82]. A systematic review of 76 studies showed that once or twice a day was better than more frequent dosing (compliance with one dose = 79% ± 14%; two doses = 69% ± 15%; three doses = 65% ± 16%; four doses = 51% ± 20% ($P < 0.001$ among dose schedules, no significant difference between one and two doses) [83].

The principal factors associated with nonadherence for HAART appear to be mainly patient-related, including homelessness and substance and alcohol abuse, reflecting the types of individuals affected by HIV [84]. Other factors may also contribute, such as inconvenient dosing frequency, dietary restrictions, pill burden, side effects [85], patient healthcare provider relationships, and the system of care [86].

A systematic review on the effectiveness of patient support and education to improve adherence to HAART identified 19 RCTs involving 2159 participants [87]. Study interventions included cognitive behavioral therapy, motivational interviewing, medication management strategies, and interventions indirectly targeting adherence, such as programs to reduce risky sexual behaviors. There is evidence that interventions targeting practical medication management skills and those delivered over at least 12 weeks were associated with improved adherence. Interventions administered to individuals were more effective than group interventions. There was no evidence that interventions targeting women or patients with a history of alcoholic abuse were effective. Overall, effective adherence interventions have not been shown to be associated with improved virologic or immunologic outcomes.

Toxicity

Toxicity is also a determinant of a successful regimen both in terms of tolerability and adherence. Liver enzyme elevation (LEE) defined as transaminases greater than five times baseline or >100 IU/L is commonly observed after combination HAART is begun. Potential risk factors after treatment with ritonavir and saquinavir with or without stavudine were investigated in 208 HIV-infected patients, by use of the Cox proportional hazard model: 18 patients (9%) developed LEE during the 48-week follow-up. Multivariate analysis, adjusted for baseline levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), showed that hepatitis B surface antigen (HBsAg) positivity (RR 8.8; 95% CI 3.3–23.1) and the use of stavudine (RR 4.9; 95% CI 1.5–16.0) were the only significant risk factors for developing LEE. After LEE occurred, ALT and AST concentrations decreased by >50% in 13 of 14 patients who continued antiretroviral treatment during LEE. Therefore, in this study, it appeared safe to continue treatment during LEE; however, more data from larger studies are required to confirm this finding [88].

In a retrospective study 65 patients taking HAART were evaluated and 24 were identified to have antiretroviral hepatotoxicity [89]. Patients older than 40 years had a 7-fold increased risk (RR 6.9; 95% CI 1.7–27.3) and those with an absolute CD4 count of <310 cells/mm^3 had a 10-fold increased risk (RR 10.2; 95% CI 2.5–41.9) for antiretroviral hepatotoxicity, in comparison with those who were younger or who had a greater absolute CD4 count. Coexisting hepatitis C infection ($P = 0.035$) was significantly associated with hepatotoxicity; of the eight patients documented to have coexisting hepatitis C infection, six (75%) were in the antiretroviral hepatotoxicity group.

In another retrospective study of 394 patients 7% were HBsAg-positive and 14% were anti-HCV-positive [90]. Patients with chronic hepatitis had a higher risk for LEE compared with patients without coinfection: 37% versus 12% respectively. After adjustment for higher baseline transaminases, the presence of HBsAg or anti-HCV remained associated with an increased risk of LEE (RR 2.78; 95% CI 1.50–5.16 and RR 2.46; 95% CI 1.43–4.24, respectively). In patients with LEE, transaminases declined whether HAART was continued or modified. Of patients with chronic HBV infection 38% lost HBeAg or developed anti-HBe after

initiation of HAART, and one seroconverted from HBsAg-positive to anti-HBs-positive. However, there was no clear relationship with LEE.

In the Swiss cohort, a prospective analysis revealed 1157 patients (37.2%) were coinfected with HCV, 1015 of whom (87.7%) had a history of intravenous drug use [91]. In multivariate Cox's regression, the probability of progression to a new AIDS-defining clinical event or to death was independently associated with HCV seropositivity (HR 1.7; 95% CI 1.26–2.30), and with active intravenous drug use (HR 1.38; 95% CI 1.02–1.88). Virologic response to HAART and the probability of treatment change were not associated with HCV serostatus. In contrast, HCV seropositivity was associated with a smaller CD4 cell recovery (HR for a CD4 cell count increase of at least 50 cells/mm^3 = 0.79; 95% CI 0.72–0.87).

There is a significantly elevated risk of severe liver disease in persons who are coinfected with HIV and HCV. A metaanalysis to quantify the effect of HIV coinfection on progressive liver disease in persons with HCV revealed eight studies that included outcomes of histologic cirrhosis or decompensated liver disease [92]. These studies yielded a combined adjusted RR of 2.92 (95% CI 1.70–5.01). Studies that examined decompensated liver disease had a combined RR of 6.14 (95% CI 2.86–13.20), whereas studies that examined histologic cirrhosis had a pooled RR of 2.07 (95% CI 1.40–3.07). The PRESCO study suggested that responses to therapy with pegylated interferon and high-dose (1000–1200 mg daily) ribavirin could approach those in non HIV-infected patients and, as had been previously observed, were dependent on HCV genotype [93,94].

Summary

There is no randomized trial evidence as to which drug regimen is most efficacious clinically. There is convincing evidence that three drugs are better than two or one. There has been considerable interest in the use of four drugs as part of an induction/maintenance approach but this has not been widely adopted. Potential increase in potency with four agents needs to be balanced against increased side effects, and there is no convincing body of evidence to support this approach at present. Dual nucleosides are the standard backbone in HAART. There seems to be little to choose between NNRTIs and boosted PIs when considering the third agent, although efavirenz seems to be better tolerated with more durable viral suppression than ritonavir-boosted lopinavir.

Adherence to HAART is critically important and, to facilitate this, drug regimens are becoming simpler, many with once-a-day drugs and no food or fluid restrictions. Once-a-day medications can be given as directly observed therapy combined, for example, with methadone [95] although there are important interactions with methadone and HAART [96]. There is still no consensus on how best to measure adherence. The studies to try to improve adherence through social means and education have been disappointing. Hepatotoxicity remains a challenge especially in the many patients who have coexisting liver disease and may be taking other hepatotoxic drugs. There is a high incidence of substance abuse and psychiatric illness amongst HIV-positive patients, which complicates the ability to take treatment [97].

Opportunistic infection prophylaxis

Although the risk of opportunistic infection has fallen in recent years it increases dramatically once a patient's CD4 count is less than 200 cells/mm^3 [47]. In the UK around 50% of patients present with a CD4 $<$350 cells/mm^3 and 30% with a CD4 $<$200 cells/mm^3 [98].

Prophylaxis for PCP

There have been two systematic reviews: Ioannidis et al. searching in 1995 and covering 35 RCTs [99] and Bucher et al. from 1997 [100] covering 22 trials. Both of these were before the widespread introduction of HAART. Since then the incidence of OIs in HIV patients has fallen so much that further studies are unlikely [101,102]. The main focus recently has been on stopping prophylaxis after immune restoration.

The first systematic review found that prophylaxis with co-trimoxazole or aerosolized pentamidine reduced the incidence of PCP more than placebo (RR 0.32; 95% CI 0.23–0.46) and that co-trimoxazole was more effective at preventing PCP than aerosolized pentamidine (RR 0.58; 95% CI 0.45–0.75) [99]. The second review found that co-trimoxazole was significantly more effective in preventing PCP than dapsone/pyrimethamine (RR 0.49; 95% CI 0.26–0.92) [100]. While the second review also showed that

co-trimoxazole compared with dapsone (with or without pyrimethamine) was more effective, the result did not reach statistical significance (RR 0.61; 95% CI 0.34–1.10) [99].

There is no significant difference in the rate of PCP infection between lower dose (160/800 mg three times weekly or 80/400 mg daily) and higher dose (160/800 mg daily) co-trimoxazole although severe adverse effects (predominantly rash, fever, and hematologic effects leading to discontinuation within 1 year) occurred in more people taking higher doses of co-trimoxazole than lower doses (25% vs 15%) [99]. One subsequent RCT (2625 people) also found no significant difference in the rate of PCP infection in people receiving co-trimoxazole 160/800 mg daily compared with three times weekly (3.5 vs 4 per 100 person-years) [103]. Discontinuation because of adverse effects was significantly more common in people taking higher doses of co-trimoxazole (RR 2.14; $P < 0.001$).

One RCT of 545 people in sub-Saharan Africa with symptomatic disease (second or third clinical stage disease in the WHO staging system) regardless of CD4 cell count, comparing co-trimoxazole with placebo, found no significant difference in incidence of PCP or toxoplasmosis. Patients taking co-trimoxazole were less likely to suffer a serious event (death or hospital admission, irrespective of the cause) than those on placebo regardless of their initial CD4 cell count (84 vs 124; HR 0.57; 95% CI 0.43–0.75; $P < 0.001$). This implies that in Africa the effect of co-trimoxazole is on preventing bacterial infections, not PCP [104].

Summary

Systematic reviews have found that co-trimoxazole is the most effective prophylactic agent for PCP.

Adverse reactions

Case presentation 4 (continued)

He is started on co-trimoxazole initially. He develops a widespread maculopapular rash with nausea and vomiting. A diagnosis of co-trimoxazole hypersensitivity is made. What are the options for patients who cannot tolerate TMX/SMX?

The gradual initiation of co-trimoxazole may improve tolerance of the regimen (17% vs 33% at 12 weeks) [105]. Two RCTs (238 people; 50 people) found no significant benefit from acetylcysteine in preventing co-trimoxazole hypersensitivity reactions in HIV-infected people [106,107].

Atovaquone, dapsone and aerosolized pentamidine are effective in persons intolerant of co-trimoxazole. There is one RCT of atovaquone in 1057 people intolerant of co-trimoxazole, of whom 298 had a history of PCP [108]. When compared with dapsone there was no significant difference between atovaquone 1500 mg daily compared with dapsone 100 mg daily (15.7 vs 18.4 cases of PCP per 100 person-years; $P = 0.20$). The overall risk of stopping treatment because of adverse effects was similar in the two arms (RR 0.94; 95% CI 0.74–1.19). One RCT with 549 people intolerant of co-trimoxazole compared high-dose with low-dose atovaquone (1500 mg daily vs 750 mg daily) with monthly aerosolized pentamidine (300 mg). It found no significant difference between the groups in the incidence of PCP (26% vs 22% vs 17%) or mortality (20% vs 13% vs 18%) after a median follow-up of 11.3 months [109].

A metaanalysis of 16 trials with 4267 patients evaluating dapsone toxicity found no significant difference in mortality for dapsone (OR for mortality for dapsone vs other primary prophylaxis 1.11; 95% CI 0.96–1.29) [110,111]. Detels el al. found that adverse effects were dose-related for dapsone (low vs high dose: 29% vs 12%) [111].

Azithromycin, rifabutin, and both drugs in combination, added to standard PCP prophylaxis were compared in an RCT. Azithromycin, either alone or in combination with rifabutin, reduced the risk of developing PCP by 45% when compared with rifabutin alone ($P = 0.008$) [112]. Gastrointestinal side effects are common with azithromycin, but they are usually mild and do not lead to stopping treatment when used for mycobacterial infection. The addition of rifabutin significantly increased the risk of stopping treatment (RR 1.67; $P = 0.03$) [113].

Concomitant coverage for toxoplasmosis

Co-trimoxazole was more effective at preventing toxoplasmosis than aerosolized pentamidine (RR 0.78; 95% CI 0.55–1.11), but there was no significant difference between co-trimoxazole and dapsone/

pyrimethamine (RR 1.17; 95% CI 0.68–2.04) [100]. Toxoplasmosis risk is probably clinically meaningful only with CD4 $<$ 100 cells/mm^3 and positive toxoplasma serology [114].

Case presentation 4 (continued)

The patient is commenced on dapsone and then 2 weeks later zidovudine, lamivudine, and efavirenz. His viral load falls to undetectable and CD4 count climbs to 320 cells/mm^3 within 6 months. He has some problems with recurrent cold sores. You wonder how to manage his herpes infection and when his PCP prophylaxis can be safely stopped.

Treatment of herpes simplex

Famciclovir and valacyclovir are effective for the suppression of herpes simplex virus (HSV) reactivation [115,116] and valacyclovir has been shown to be equivalent to acyclovir [117].

Stopping *Pneumocystis* prophylaxis

In the metaanalysis of 14 randomized and nonrandomized studies with 3584 subjects who had discontinued prophylaxis when their CD4 count was sustained $>$200 cells/mm^3 for 3 months, eight cases of PCP occurred during 3449 person-years (0.23 cases per 100 person-years; 95% CI 0.10–0.46) [118]. In the decision analysis, mortality and time spent alive without immunodeficiency in the modeled discontinuation strategy were similar to those in the continuation strategy. For patients who received primary prophylaxis, the discontinuation strategy led to slightly fewer episodes of PCP and fewer toxicity-related prophylaxis withdrawals (8.6 vs 34.5 cases per 100 patients during a 10-year period). Comparative results were similar for patients on secondary prophylaxis. The review found a low incidence of PCP in people discontinuing both primary and secondary prophylaxis after a mean of 1.5 years (7/3035 [0.23%] with discontinuing primary prophylaxis and 1/549 [0.18%] discontinuing secondary prophylaxis; mean annual incidence over 1.5 years 0.23%; 95% CI 0.10–0.46%; no statistical heterogeneity among studies). Neither of the two RCTs identified in the review found any cases of PCP after discontinuation [119,120]. A total of 146 patients were enrolled in a randomized study of stopping secondary prophylaxis (77 in the treatment discontinuation arm). After $>$2 years, one definitive and one presumptive case of PCP were observed, both of which occurred in patients who discontinued therapy [121].

Prophylaxis for PCP was withdrawn in 524 patients (426 primary and 98 secondary prophylaxis), prophylaxis for *Mycobacterium avium* complex (MAC) was withdrawn in 28 patients (13 primary and 15 secondary), and prophylaxis for cytomegalovirus (CMV) retinitis was withdrawn in 10 patients [122]. CD4 counts were generally maintained above accepted prophylaxis threshold levels during the period of follow-up (95–98% of the time). Total follow-up to last report or reinitiation of prophylaxis was 680 and 144 person-years for patients discontinuing primary and secondary PCP prophylaxis, respectively. No cases of PCP were reported, giving incidence rates of 0.0 (upper 95% confidence limit 0.4) and 0.0 (2.1) per 100 person-years. No cases of MAC were reported, but one patient had a recurrence of CMV retinitis. PCP prophylaxis was restarted in 30 patients; no patients restarted MAC or CMV prophylaxis.

Nineteen patients with suppressed viral loads but CD4 counts below 200 cells/mm^3 were followed after prophylaxis was discontinued. Eleven had been taking daily TMP-SMX, seven were receiving monthly aerosolized pentamidine, and one patient never received any prophylaxis [123]. The median CD4 count at the time of discontinuation and at the most recent determination was 120 (range 34–184) and 138 (range 6–201) cells/mm^3 respectively. At the time of reporting, patients had been off PCP prophylaxis for a median of 9.0 (range 3–39) months (261 patient-months). No patient developed PCP. This is significantly different from the risk of developing PCP with a CD4 count of $<$200 cells/mm^3 in untreated HIV infection (rate difference 9.2%; 95% CI 5.7–12.8%; $P < 0.05$).

There is also no change in incidence of other bacterial infections after stopping prophylaxis [124].

Toxoplasmosis

There are three RCTs. The first, which was included in the systematic review, found no cases of toxoplasma encephalitis at 6 months in people discontinuing prophylaxis (see PCP above) [120]. The second RCT (302 people with a satisfactory response to HAART) compared discontinuation with continuation of toxoplasma

prophylaxis [125]. After a median of 10 months it found no episodes of toxoplasma encephalitis in either group.

The efficacy of a thrice-weekly regimen was similar to that of a daily regimen in the prevention of relapses of toxoplasma encephalitis in a RCT in 124 Spanish patients. Administration of antiretroviral therapy was the only factor associated with a lower incidence of relapse [126].

Case presentation 4 (continued)

He returns after 6 months with CD4 now 400 cells/mm^3 and viral load undetectable. However after the death of a close friend it soon becomes apparent that he has developed a chaotic lifestyle, abusing substances, and has problems with taking regular medication. He decides not to attend the clinic for a while and is lost to follow-up. After 3 years he returns with a CD4 count of 50 cells/mm^3 and an increasing viral load. He has been intermittently attending another clinic and his current medication is stavudine, didanosine, abacavir, ritonavir, and fosamprenavir. Viral resistance testing, viral phenotyping, and therapeutic drug monitoring may be used to guide therapy in this circumstance but the situation is far from clear.

Genotypic resistance testing

There are three RCTs showing a benefit of genotypic resistance testing plus expert advice for patients failing HAART. A total of 326 HIV-1-infected patients on stable HAART with virologic failure were studied. The baseline CD4 cell count and plasma HIV-1 RNA were 387 ($\pm$224) cells/mm^3 and 4 ($\pm$1) log respectively. The proportion of patients with plasma HIV-1 RNA $<$ 400 copies/mL at 24 weeks differed between genotyping and no genotyping arms (48.5 and 36.2%; $P < 0.05$). Factors associated with a higher probability of plasma HIV-1 RNA $<$ 400 copies/mL were HIV-1 genotyping (OR 1.7; 95% CI 1.1–2.8; $P = 0.016$) and the expert advice in patients failing a second-line HAART (OR 3.2; 95% CI 1.2–8.3; $P = 0.016$) [127].

To compare standard care (control, $n = 43$) or treatment according to the resistance mutations in protease and reverse transcriptase genes (genotypic group, $n = 65$), 108 patients were enrolled in the VIRADAPT study [128]. At month 3, the mean change in HIV-1 RNA was -1.04 log in the study group compared with -0.46 log in the control group (mean difference 0.58 log; 95% CI 0.14–1.02; $P = 0.01$). At month 6, changes were 1.15 (0.15) log copies/mL, and 0.67 (0.19) log copies/mL in the genotypic group and the control group, respectively (mean difference 0.48 log; $P = 0.05$). At month 3, HIV-1 RNA was lower than detection level (200 copies/mL) in 29% (19/65) of patients in the genotypic group versus 14% (6/43) in the control group ($P = 0.017$). At month 6, the values were 32% (21/65) and 14% (6/43) ($P = 0.067$) for the genotypic group and the control group, respectively. Therapy was generally well tolerated, with 10 patients (six in the genotypic group, four in the control group) requiring toxic effect-related drug modification.

In the genotypic antiretroviral resistance testing (GART) study, 153 HIV-infected adults, with a 3-fold or greater rise in plasma HIV-1 RNA on at least 16 weeks of combination HAART, were randomized either to a GART group, where genotype interpretation and suggested regimens were provided to clinicians, or to a no-GART group, where treatment choices were made without such input [129]. HIV-1 RNA, averaged at 4 and 8 weeks following randomization, decreased by 1.19 log for the 78 GART patients and 0.61 log for the 75 no-GART patients (treatment difference: 0.53 log; 95% CI 0.77, 0.29; $P = 0.00001$). Overall, the best virologic responses occurred in patients who received three or more drugs to which their HIV-1 appeared to be susceptible. A note of caution is given here as discrepant results in "expert" interpretation of genotype resistance data have been shown [130].

In the CREST study 327 patients completing $\geqslant$1 month of follow-up were included in a randomized, open-label trial over 48 weeks to receive a genotype (group A) or genotype plus virtual phenotype (group B) prior to selection of their regimen [131]. At 48 weeks, there were no significant differences between the groups for mean change from baseline plasma HIV RNA (group A: 0.68 log copies/mL, group B: 0.58 log copies/mL; $P = 0.23$) and mean change from baseline CD4+ cell count (group A: 37 cells/mm^3, group B: 50 cells/mm^3; $P = 0.28$).

Viral phenotyping

A total of 272 subjects who failed to achieve or maintain virologic suppression (HIV-1 RNA plasma level

>2000 copies/mL) with previous exposure to two or more nucleoside reverse transcriptase inhibitors and one protease inhibitor were randomized to HAART guided by phenotyping or standard of care [132]. At week 16, using intent-to-treat (ITT) analysis, a greater proportion of subjects had HIV-1 RNA levels < 400 copies/mL in the phenotyping than in the standard-of-care arm ($P = 0.036$, ITT observed; $P = 0.079$, ITT missing equals failure). Subjects in the phenotyping arm had a significantly greater median reduction in HIV-1 RNA levels from baseline than the standard-of-care arm ($P = 0.005$ for 400 copies/mL; $P = 0.049$ for 50 copies/mL assay detection limit). Significantly more subjects in the phenotyping arm were treated with two or more "active" antiretroviral agents than in the standard-of-care arm ($P = 0.003$).

Therapeutic drug monitoring

There are no randomized controlled data to support therapeutic drug monitoring but, in a pharmacologic substudy of VIRADAPT, the impact of plasma protease inhibitor trough levels on changes in HIV RNA were assessed in 81 patients treated with genotypic-guided therapy [133]. Linear regression analysis showed a significant relationship between PI concentration and HIV RNA in the plasma. "Suboptimal" concentration (SOC) was defined as at least two PI plasma levels <2 times IC95 and patients were categorized into four groups: G1 (SOC/control), G2 (OC/control), G3 (SOC/genotype), and G4 (OC/genotype). OC and SOC were found in 67.9% (55/81) and 32.1% (26/81) of patients, respectively. Mean changes in HIV RNA from baseline at month 6 were: -0.23 ± 0.29 log copies/mL (G1); -0.97 ± 0.28 (G2); -0.68 ± 0.37 (G3); -1.38 ± 0.20 (G4). Multivariate analysis showed PI plasma concentrations to be an independent predictor of HIV-RNA evolution ($P = 0.017$).

Management of multiple resistance

The recent BHIVA guidelines addressing this question have three sections – continue, change, or interrupt – but there is no consensus at present [10]. There is evidence from recent trials of new agents that the more active drugs that are available to include in a new regimen in MDR-HIV the better [134,135]. There are an increasing number of new drugs and indeed new classes of drug which are active against MDR-HIV.

There is evidence of increasing accumulation of resistance mutations in continuing a failing regimen. In one study of patients with viral load >200 copies/mL, the average increase per year in the number of mutations was 0.5 for reverse transcriptase (RT) mutations, 0.2 for major PI mutations and 0.3 for minor PI mutations [136].

Structured treatment interruption

Small studies have shown conflicting results for structured treatment interruptions (STI) on surrogate markers, which may be explained by the length of the treatment interruption (on average 8–16 weeks) or on the number of drugs commenced after it (so called mega or giga HAART) [137–139]. There is a multinational clinical trial (OPTIMA) looking at the options in management with antiretrovirals in these so-called salvage therapy patients.

Other clinical trials have shown no benefit. A total of 147 patients were randomized in a Canadian study [140]: 79 to the immediate switch (IS) arm and 68 to the STI arm. Success was achieved by 64% in the IS arm and 51% in the STI arm (95% confidence interval for the difference from 5% in favor of STI to 30% in favor of IS). During the STI, the median decrease in CD4 count was 80 cells/mm and the increase in viral load was 0.8 $\log_{10}$ copies/mL. There were no differences in median CD4 cell counts or HIV RNA levels at week 60. Two unrelated deaths (one in each arm) and three AIDS-defining events (in the STI arm) occurred.

A metaanalysis of 17 studies confirmed a lack of benefit as far as virologic or immunologic endpoints were concerned [141]. There is evidence from the large EUROSIDA cohort that even at low CD4 counts there is a benefit from not stopping therapy [142] and the SMART study has highlighted the increased hazard associated with treatment interruption at any CD4 count [143].

As an interim measure, double boosted PIs have shown some promise in virologic improvement in selected patients [144] as has lamivudine monotherapy [145]. Nucleoside analogs often exert continued antiviral activity in the setting of drug-resistance mutations and both nucleoside analogs and PIs can select for drug-resistance mutations that reduce viral

fitness [146]. These strategies need to be investigated further in clinical trials.

Summary

The strategy of treatment interruption is not recommended outside of the setting of a clinical trial. However there may be benefits for patients other than virologic improvement including quality of life and improved adherence with the next regimen, and there does not seem to be much harm to patients as long as they are closely monitored and given appropriate OI prophylaxis.

Treatment and prophylaxis of opportunistic infections (continued)

Case presentation 4 (continued)

The patient decides not to continue with therapy and is adamant that he no longer wants any in the future. He is admitted with increasing confusion, fever, and neck stiffness. Fundoscopy reveals CMV retinitis but no papilledema. His CD4 count is 10 cells/mm^3. You consider the possible conditions he is at risk of and how best to manage him.

Table 11.1 lists the usual pathogens related to CD4 count.

Cryptococcal meningitis needs to be excluded by lumbar puncture and staining of cerebrospinal fluid (CSF) with Indian ink.

Case presentation 4 (continued)

The opening pressure is 30 mm of CSF, and CSF is positive for *Cryptococcus* with a white cell count of 115, mainly lymphocytes; a CSF protein of 2.4 g/dL (range −1.6 g/dL), and a glucose of 0.6 mmol/L. A diagnosis of cryptococcal meningitis is made.

Treatment of cryptococcal meningitis

In a double-blind multicenter study, patients with a first episode of AIDS-associated cryptococcal meningitis were randomly assigned to treatment with higher dose amphotericin B (0.7 mg/kg per day) with or without flucytosine (100 mg/kg per day) for 2 weeks (step 1), followed by 8 weeks of treatment with itraconazole (400 mg per day) or fluconazole (400 mg per day) (step 2) [147]. At 2 weeks, the CSF cultures were negative in 60% of the 202 patients receiving amphotericin B plus flucytosine and in 51% of the 179 receiving amphotericin B alone ($P = 0.06$). The clinical outcome did not differ significantly between the two groups. Overall mortality was 5.5% in the first 2 weeks and 3.9% in the next 8 weeks, with no significant difference between the groups. In a multivariate analysis, the addition of flucytosine during the initial 2 weeks and treatment with fluconazole for the next 8 weeks were independently associated with CSF sterilization. As a result standard guidelines for treatment of cryptococcal meningitis recommend 2 weeks of amphotericin B at a dose of 0.7 mg/kg per day (with flucytosine) followed by fluconazole at a dose of 400 mg per day for another 8 weeks.

There is one direct comparison between amphotericin B deoxycholate (0.7 mg/kg per day) and liposomal amphotericin (AmBisome) (4 mg/kg per day) in 27 patients showing that AmBisome therapy resulted in earlier negative CSF cultures [148]. The liposomal amphotericin was less nephrotoxic and this has been confirmed in other studies in HIV-positive patients [149].

In a randomized trial comparing amphotericin B and fluconazole, treatment was successful in 25 of the 63 amphotericin B recipients (40%; 95% CI 26–53) and in 44 of the 131 fluconazole recipients (34%; 95% CI 25–42%; $P = 0.40$) [150]. There was no significant difference between the groups in overall mortality owing to cryptococcosis (amphotericin vs fluconazole, 9 of 63 [4%] vs 24 of 131 [8%]; $P = 0.48$); however, mortality during the first 2 weeks of therapy was higher in the fluconazole group (15% vs 8%; $P = 0.25$). Multivariate analyses identified abnormal mental status (lethargy, somnolence, or obtundation) as the most important predictive factor of death during therapy ($P < 0.0001$). In Africa 30 patients were randomized to receive combination therapy with fluconazole, 200 mg once a day for 2 months, and flucytosine, 150 mg/kg per day) for the first 2 weeks, and 28 to receive fluconazole alone. Patients in both groups who survived for 2 months continued fluconazole as maintenance therapy at a dose of 200 mg three times per week for 4 months. The combination therapy prevented death within 2 weeks and significantly

Table 11.1 Pathogens related to CD4 counts

CD4 count	Infection	Noninfectious complications
>500	Acute HIV syndrome	Progressive generalized lymphadenopathy
	Candida vaginitis	Polymyositis
		Aseptic meningitis
		Guillain–Barré syndrome
200–500	Pneumococcal and other bacterial pneumonia	Carcinoma in situ
	Pulmonary tuberculosis	Cervical cancer
	Kaposi sarcoma	Lymphocytic interstitial pneumonitis
	Herpes zoster	Mononeuritis multiplex
	Thrush	Anemia
	Cryptosporidiosis, self-limiting	Idiopathic thrombocytopenia purpura
	Oral hairy leukoplakia	
<200	*Pnemocystis carinii* pneumonia	Wasting
	Candida esophagitis	B-cell lymphoma
	Disseminated/chronic herpes simplex	Cardiomyopathy
	Toxoplasmosis	Peripheral neuropathy
	Cryptococcosis	HIV-associated dementia
	Disseminated histoplasmosis	CNS lymphoma
	Disseminated coccidiomycosis	HIV-associated nephropathy
	Chronic cryptosporidiosis	
	Progressive multifocal leukoencephalopathy (PMLE)	
	Microsporidiosis	
	Miliary/extrapulmonary tuberculosis	
<50	CMV disease	
	Disseminated *Mycobacteruim avium* complex	

increased the survival rate among patients (32%) at 6 months over that among patients receiving monotherapy (12%) ($P = 0.022$) [151].

Oral itraconazole (200 mg twice a day) for 6 weeks was less effective than amphotericin B (0.3 mg/kg per day) plus flucytosine (150 mg/kg daily) in 28 patients [152].

The importance of controlling the raised intracranial pressure associated with cryptococcal meningitis by repeated lumbar puncture or CSF drainage was established in a retrospective analysis of 221 patients in the van der Horst study [147]. After receiving antifungal therapy, those patients whose CSF pressure was reduced by >10 mm or did not change had more frequent clinical response at 2 weeks than did those whose pressure increased >10 mm ($P = 0.001$). Patients with pretreatment opening pressure of <250 mm had increased short-term survival compared with those with higher pressure [153]. This was confirmed in a small prospective study of 10 patients with raised ICP treated with CSF drainage [154].

Prophylaxis against fungal infection

Five studies were identified in a Cochrane review of interventions for the primary prevention of cryptococcal disease [155]. The authors concluded that prophylaxis with either itraconazole or fluconazole was effective (RR 0.21, 95% CI 0.09, 0.46 compared with placebo; $n = 1316$), however neither had a clear effect on overall mortality. One RCT found that itraconazole reduced relapses of successfully treated cryptococcal meningitis more than fluconazole (13/57 [23%] vs 2/51 [4%]; ARR 19%, 95% CI 6.2–31.7; RR 0.17, 95% CI 0.04–0.71; NNT 5, 95% CI 3–16). The trial was stopped early because of the higher rate of relapse with fluconazole [156].

A Cochrane review included 9 studies of interventions for the prevention of oropharyngeal candidiasis [157]. Fluconazole was effective in preventing clinical episodes compared with placebo (RR 0.61; 95% CI 0.5–0.74) and compared with no treatment (RR 0.16; 95% CI 0.08–0.34). In a RCT comparing dosing regimen, there was no difference in the rate of invasive fungal infections between fluconazole 200 mg daily with 400 mg once weekly over a follow-up of 74 weeks (8% vs 6%; ARR 2.2%, 95% CI −1.7% to 6.1) [158]. However, the incidence of candidiasis was twice as common in people taking the weekly dose.

In a RCT, fluconazole reduced the incidence of invasive fungal disease and mucocutaneous candidal infections compared with clotrimazole (4% vs 11%; RH 3.3; 95% CI 1.5–7.6) [159]. In HIV patients with candidiasis treated with itraconazole, relapse was reduced with itraconazole prophylaxis (5/24 [21%] with itraconazole vs 14/20 [70%] with placebo; ARR 49%, 95% CI 19–64; NNT 2, 95% CI 2–5), and the time interval before relapse occurred was increased (median time to relapse: itraconazole 8.0 weeks vs placebo 10.4 weeks, $P = 0.001$) [160].

There is one open-label uncontrolled study (44 people), which found that itraconazole may be effective in preventing the relapse of histoplasmosis [161].

Mycobacterium avium complex

Treatment

HIV-positive patients ($n = 246$) with disseminated *Mycobacterium avium* complex (MAC) received either azithromycin 250 mg every day, azithromycin 600 mg every day, or clarithromycin 500 mg twice a day, each combined with ethambutol, for 24 weeks. The azithromycin 250 mg arm of the study was dropped after an interim analysis showed a lower rate of clearance of bacteremia. At 24 weeks of therapy, the likelihood of patients developing two consecutive negative cultures (46% vs 56%; $P = 0.24$) or one negative culture (59% vs 61%; $P = 0.80$) was similar for azithromycin 600 mg ($n = 68$) and clarithromycin ($n = 57$), respectively. The likelihood of relapse was 39% versus 27% ($P = 0.21$) on azithromycin compared with clarithromycin, respectively. Of the six patients who experienced relapse, none of those randomized to receive azithromycin developed isolates resistant to macrolides, compared with two of three patients randomized to receive clarithromycin. Mortality was similar in patients comprising each arm of the study (69% vs 63%; HR 1.1, 95% CI 0.7–1.7) [162].

AIDS patients with disseminated MAC disease ($n = 85$) were randomized to receive a three-drug regimen of clarithromycin, rifabutin or clofazimine, and ethambutol. Two dosages of clarithromycin, 500 or 1000 mg twice daily, were compared [163]. After a mean follow-up of 4.5 months, 10 (22%) of 45 patients receiving clarithromycin at 500 mg twice daily had died (70 deaths per 100 person-years) compared with 17 (43%) of 40 patients receiving clarithromycin at 1000 mg twice daily (158 deaths per 100 person-years) (RR 2.43, 95% CI 1.11–5.34; $P = 0.02$). After 10.4 months, 20 (49%) of 41 patients receiving rifabutin had died (81 deaths per 100 person-years) compared with 23 (52%) of 44 patients receiving clofazimine (94 deaths per 100 person-years) (RR 1.20, 95% CI 0.65–2.19; $P = 0.56$). Bacteriologic outcomes were similar among treatment groups. In treating MAC disease in AIDS patients, the recommended maximum dose of clarithromycin is 500 mg twice daily.

The effect of two regimens for treatment of MAC bacteremia in an HIV-positive population on symptoms and health status outcomes were evaluated using a substudy of an open-label RCT comparing rifampin 600 mg plus ethambutol 15 mg/kg daily plus clofazimine 100 mg daily plus ciprofloxacin 750 mg twice daily (four-drug arm), with rifabutin 600 mg daily (amended to 300 mg daily in mid-trial) plus ethambutol 15 mg/kg daily plus clarithromycin 1000 mg twice daily (three-drug arm). The primary health status outcome was the change on the 8-item symptom subscale of the Medical Outcome Study (MOS)-HIV Health Survey adapted for MAC. Patients on the three-drug arm had better Karnofsky score at 16 weeks ($P = 0.001$) and better outcomes on the social function, mental health, energy/fatigue, health distress, and cognitive function subscales of the MOS-HIV. The three-drug arm was superior to the four-drug arm in terms of impact on MAC-associated symptoms, functional status, and other aspects of health status [164].

Prophylaxis

Prospective cohort studies have found that the risk of disseminated MAC disease increases substantially with a lower CD4 count but was clinically important only for CD4 <50 cells/mm^3 [114].

Azithomycin and clarithromycin

There is one systematic review (search date 1997) of prophylaxis and treatment of MAC [165]. It identified one RCT (682 people with advanced AIDS) that found that clarithromycin compared with placebo significantly reduced the incidence of MAC (6% vs 16%; HR 0.31, 95% CI 0.18–0.53). It found no significant difference in the death rate (32% vs 41%; HR 0.75, $P = 0.026$). Adverse effects led to discontinuation of treatment in slightly more people taking clarithromycin than placebo (8% vs 6%; $P = 0.45$).

Azithromycin once weekly reduced the incidence of MAC more than placebo (11% vs 25%; $P = 0.004$). Gastrointestinal side effects were more likely with azithromycin than with placebo (71/90 [79%] vs 25/91 [28%]; number needed to harm [NNH] 2), but they were rarely severe enough to cause discontinuation of treatment (8% vs 2% in the two arms; $p = 0.14$) [166].

Other combinations

One RCT (1178 people with AIDS) compared rifabutin versus clarithromycin versus clarithromycin plus rifabutin [167]. The risk of MAC was significantly reduced in the clarithromycin alone group (relative risk reduction [RRR] 44% for clarithromycin vs rifabutin; $P = 0.005$) and the combination group when compared with rifabutin alone (RRR 57% for combination vs rifabutin; $P = 0.0003$). There was no significant difference in the risk of MAC between the combination and clarithromycin arms ($P = 0.36$).

The combination of azithromycin plus rifabutin versus azithromycin alone significantly reduced the incidence of MAC at 1 year (15.3% with rifabutin vs 7.6% for azithromycin vs 2.8% with rifabutin plus azithromycin; $P = 0.008$ for rifabutin vs azithromycin; $P = 0.03$ for combination vs azithromycin). Dose-limiting toxicity was more likely with azithromycin plus rifabutin than with azithromycin alone (HR 1.67; $P = 0.03$) [113].

Other combinations have been studied in RCTs. Clarithromycin (1000 mg daily), clofazimine, and ethambutol was associated with significantly fewer relapses of MAC than the combination of clarithromycin plus clofazimine without ethambutol (68% relapsed in the three-drug regimen vs 12% in the two-drug regimen at 36 weeks; $P = 0.004$) [168]. The addition of clofazimine to clarithromycin and ethambutol did not improve clinical response and was associated with higher mortality in the clofazimine arm (62% with clofazimine vs 38% without clofazimine; $P = 0.012$) [169]. Clarithromycin, rifabutin, and ethambutol reduced the relapse rate of MAC compared with clarithromycin plus clofazimine [170] but there was no significant difference in survival between people taking clarithromycin plus ethambutol and people taking clarithromycin plus ethambutol plus rifabutin [171].

Adverse events

Adverse events occurred in 31% of people receiving the combination of clarithromycin and rifabutin compared with 16% on clarithromycin alone and 18% on rifabutin alone ($P = 0.001$) [165]. Uveitis occurred in 42 people: 33 were on clarithromycin plus rifabutin, seven were on rifabutin alone, and two were on clarithromycin alone. In a review of 54 people with rifabutin-associated uveitis, uveitis was dose dependent, occurred from 2 weeks to more than 7 months after initiation of rifabutin treatment, and was more likely in people taking rifabutin and clarithromycin [172]. Combinations of drugs may lead to increased toxicity and mortality[163,169]. Optic neuropathy may occur with ethambutol, but has not been reported in RCTs in people with HIV where the dose and symptoms were carefully monitored.

Stopping prophylaxis

In 643 HIV-1-infected patients, with a previous CD4 cell count <50 cells/mm^3 and a sustained increase to >100 cells/mm^3 during HAART, given azithromycin 1200 mg once weekly ($n = 321$), or matching placebo ($n = 322$), there were two cases of MAC infection among the 321 patients assigned to placebo (incidence rate, 0.5 events per 100 person-years; 95% CI 0.06–1.83 events per 100 person-years) compared with no cases among the 322 patients assigned to azithromycin (95% CI 0–0.92 events per 100 person-years), resulting in a treatment difference of 0.5 events per 100 person-years (95% CI 0.20–1.21 events per 100 person-years) for placebo versus azithromycin. Both cases were atypical in that MAC was localized to the vertebral spine. Patients receiving azithromycin were more likely than those receiving placebo to discontinue treatment with the study drug permanently because of adverse events (8% vs 2%; HR 0.24, 95% CI 0.10–0.57) [173].

A second RCT compared azithromycin with placebo in 520 people without previous MAC disease with CD4 > 100 cells/mm^3 in response to HAART. There were no episodes of confirmed MAC disease in either group over a median follow-up of 12 months [174]. Again there were more adverse effects leading to discontinuation of treatment with azithromycin than with placebo (7% vs 1%; $P = 0.002$).

Summary

RCTs have found that clarithromycin and ethambutol, with or without rifabutin, reduce the incidence of MAC. Clofazimine and high-dose clarithromycin are associated with increased mortality. Clarithromycin alone and clarithromycin plus rifabutin both reduce the incidence of MAC compared with rifabutin alone. Azithromycin plus rifabutin reduces the incidence of MAC compared with azithromycin alone but is associated with more side effects.

Cytomegalovirus infection

Treatment of cytomegalovirus

Ganciclovir and foscarnet have been the mainstays of treatment of CMV disease [175]. With the availability of oral valganciclovir, this drug was compared with intravenous ganciclovir as induction therapy for newly diagnosed CMV retinitis in 160 patients with AIDS. After 4 weeks, all patients received valganciclovir as maintenance therapy. Of the patients who could be evaluated, seven of 70 assigned to intravenous ganciclovir (10.0%) and seven of 71 assigned to oral valganciclovir (9.9%) had progression of CMV retinitis during the first 4 weeks (difference in proportions, 0.1 percentage point; 95% CI −9.7 to 10·0); 47 of 61 patients (77.0%) assigned to intravenous ganciclovir and 46 of 64 (71.9%) assigned to valganciclovir had a satisfactory response to induction therapy (difference in proportions, 5.2 percentage points; 95% CI 20.4–10.1). The median times to progression of retinitis were 125 days in the group assigned to intravenous ganciclovir and 160 days in the group assigned to oral valganciclovir. The frequency and severity of adverse events were similar in the two treatment groups [176].

Prophylaxis for cytomegalovirus

One RCT (725 people with a median CD4 count of 22 cells/mm^3) found that oral ganciclovir halved the incidence of CMV compared with placebo (event rate 16% vs 30%; $P = 0.001$) but 25% of people who did not develop CMV developed severe neutropenia and were treated with granulocyte colony-stimulating factor [177]. A second RCT (994 HIV-1-infected people with CD4 < 100 cells/mm^3 and CMV seropositivity) found no difference in the rate of CMV in people taking oral ganciclovir compared with placebo (event rates 13.1 vs 14.6 per 100 person-years; HR 0.92, 95% CI 0.65–1.27) [178]. Neither RCT found a significant difference in overall mortality.

There is one systematic review of individual patient data (eight RCTs) in people with any stage of HIV infection or AIDS [179]. It found no difference in protection against CMV disease between acyclovir compared with no treatment or placebo. However, acyclovir significantly reduced overall mortality (RR 0.81; $P = 0.04$) and HSV and varicella zoster virus (VZV) infections ($P < 0.001$ for both). One RCT (1227 CMV seropositive people with CD4 < 100 cells/mm^3) compared valaciclovir, high-dose acyclovir, and low-dose acyclovir. It found increased mortality in the valaciclovir group, which did not reach statistical significance ($P = 0.06$) and 1-year discontinuation rates of 51% for valaciclovir, 46% for high-dose acyclovir, and 41% for low-dose acyclovir [180]. The CMV rate was lower in the valaciclovir group than in the acyclovir groups (12% vs 18%; $P = 0.03$).

Stopping CMV prophylaxis

There are no RCTs or reviews. There are several small case series [181–189]. The study with the longest follow-up (mean 20.4 months) found no relapses in 41 people discontinuing maintenance treatment [181]. However, another study with mean follow-up of 14.5 months found five (29%) relapses among 17 participants who withdrew from maintenance; all of them occurred after the CD4 cell count had dropped again to <50 cells/mm^3 (8 days/10 months after this event) [184]. In one observational series, 12/14 participants (86%) had evidence of immune reconstitution retinitis even before starting withdrawal of prophylaxis [183]. Worsening uveitis was associated with a substantial vision loss (>3 lines) in three participants. It is difficult to conduct a RCT of adequate sample size to exclude modest differences in relapse rates. The observational evidence suggests that withdrawal of CMV maintenance treatment may be

considered in selected people in whom CMV disease is in remission, CD4 >100 cells/mm^3, and HIV replication remains suppressed. We found no clear evidence on whether quantification of CMV viremia should be considered in the decision to withdraw from maintenance. One small case series found that relapses were associated with a drop in the CD4 cell count [184]. However, we found no randomized or other reliable evidence of when CMV maintenance treatment should be reinstituted.

Case presentation 4 (continued)

The patient improves with amphotericin and is discharged home on oral fluconazole; however, he presents again 3 months later with increasing confusion. CT scan shows no focal lesions and CSF obtained by lumbar puncture shows neither evidence of cryptococcal infection nor any white cells. You review the causes of confusion in late HIV disease.

Other AIDS-related illness

Non-Hodgkin lymphoma

Patients with AIDS-associated lymphoma/leukemia historically have a poor prognosis and were frequently treated with low-intensity therapy. There is one RCT comparing reduced therapy with standard dose: 198 HIV-seropositive patients with previously untreated, aggressive non-Hodgkin lymphoma were randomly assigned to receive standard-dose therapy with methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone (m-BACOD) along with granulocyte-macrophage colony-stimulating factor (GM-CSF; $n = 94$) or reduced-dose m-BACOD with GM-CSF administered only as indicated ($n = 98$) [190]. A complete response was achieved in 39 of the 94 assessable patients assigned to low-dose therapy (41%) and in 42 of the 81 assessable patients assigned to standard-dose therapy (52%, $P = 0.56$). There were no significant differences in overall or disease-free survival; median survival times were 35 weeks for patients receiving low-dose therapy and 31 weeks for those receiving standard-dose therapy (RR for death in the standard-dose group = 1.17; 95% CI 0.84–1.63, $P = 0.25$). Toxic effects of chemotherapy rated grade 3 or higher occurred in 66 of 94 patients assigned to standard-dose therapy (70%) and 50 of 98 patients assigned to low-dose treatment (51%; $P = 0.008$). Hematologic toxicity accounted for the difference. In a randomized trial of risk-adapted intensive chemotherapy for AIDS related lymphoma, 5-year overall survival was associated with HAART therapy (RR 1.6, $P < 0.001$), International Prognostic Index score (RR 1.5, $P < 0.001$), and stage of HIV but not with chemotherapy regimen [191].

AIDS dementia complex

A metaanalysis of 2411 patients in the ACTG 116A, ACTG116B/117, ACTG175, BMS010, and CTN002 trials had 21 documented cases of AIDS dementia complex (ADC) during the 15-month follow-up period. The rates per 100 person-years of follow-up were 0.70, 0.65, and 0.41 for the zidovudine, high-dose didanosine, and didanosine arms, respectively. There were no significant differences in risks of ADC between treatment arms (zidovudine vs high-dose didanosine: $P = 0.30$; zidovudine vs didanosine: $P = 0.97$; didanosine vs high-dose didanosine: $P = 0.41$) [192].

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PMLE) affects about 4% of patients with AIDS, and survival after the diagnosis of leukoencephalopathy averages only about 3 months. JC virus PCR in blood has a poor positive predictive value (16%) but a good negative predictive value (96%) for PMLE [193]. However, in one study, PCR of CSF yielded sensitivity and specificity values of 100% and 90%, respectively [194].

Case presentation 4 (continued)

CSF samples are sent for JC virus PCR and this is positive. MRI scans show typical changes of PMLE. Lymph node biopsy does not show any evidence of lymphoma nor of Mycobacterium avium-intracellulare. He deteriorates further and dies in a hospice 2 months later.

In observational studies no benefit has been found using cidofovir [195] nor cytarabine administered either intravenously or intrathecally [196]. A small observational study in 27 patients found the use of cidofovir was independently associated with a reduced risk of death (HR 0.21; 95% CI 0.07–0.65, $P < 0.005$) [197].

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CHAPTER 12
Influenza

Ashley Roberts & Joanne M. Langley

Case presentation

A 66-year-old male with type 2 diabetes mellitus presents with a 2-day history of fever and cough during the month of January. He also complains of intermittent headaches, "aches and pains," and loss of appetite. He is having difficulty maintaining his usual tight glucose control during this illness. A retired schoolteacher, he just returned from a visit with his young grandchildren, all of whom had coughs, runny nose, and fever. He has no significant travel history or animal exposure. On examination, the patient looks uncomfortable and diaphoretic. His temperature is 38.5ºC, respiratory rate 25, heart rate 90, and the O_2 saturation 98% on room air. There is mild increased work of breathing and crackles bilaterally at the lung bases. The rest of his examination is normal. The chest radiograph reveals nonspecific perihilar opacities and streaking bilaterally. There is no focal consolidation.

On further questioning, the patient remembers receiving "a vaccine for pneumonia" last year. He can't specifically remember getting the influenza vaccine this year. You recall getting an email from the public health authority about an influenza virus outbreak in a nearby nursing home, and wonder if you should institute a diagnostic test for influenza in this patient. You also wonder if antiviral treatment might help this patient.

Diagnosis

Influenza occurs in epidemics of variable severity every winter in temperate climates, affecting up to 20% of the general population [1]. In tropical and subtropical climates influenza occurs throughout the year with one or more peaks of activity. Pandemic outbreaks of influenza, related to major shifts in the viral hemagglutinin (H) or neuraminidase (N) antigens, may not have this seasonal pattern; this type of influenza is not discussed here. The seasonality of interpandemic influenza incidence affects the accuracy of diagnosis. The methods for diagnosis of influenza are clinical, laboratory testing of respiratory tract specimens or serum, and diagnostic imaging. Diagnostic accuracy is highest when influenza is circulating in the community, since the pretest likelihood will be higher due to increased disease prevalence. Laboratory confirmation of influenza virus infection remains the most accurate diagnostic tool.

Clinical diagnosis

Influenza is a viral infection of the respiratory tract, which is accompanied by nonspecific systemic symptoms. Generally of acute onset, the symptoms include systemic manifestations (fever, malaise, anorexia, chills, myalgia, headache) and those specific to the respiratory tract (cough, sore throat, rhinorrhea, tachypnea, sneezing). Two systematic reviews on the diagnosis of influenza were found that included primary prospective studies where clinical signs and symptoms were compared to a gold standard diagnosis using laboratory confirmation. A review by Ebell et al. found a positive likelihood ratio (LR) >2.0 for the following individual symptoms: rigors (7.2), sweating (2.86), confined to bed (2.4), and unable to cope with daily activities (2.3) [2]. A later review, which excluded studies based on quality criteria, included only three of the seven primary studies in Ebell's review and identified three other studies [3].

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It concluded that no individual sign or symptom of influenza had a positive LR >2.0, that is, high enough to confirm influenza.

If the odds of laboratory-confirmed influenza in a patient without certain individual symptoms (i.e., negative LR) are <0.5 then it is likely that influenza can be ruled out [3]. In the first review [2] four individual symptoms had LR <0.50, indicating that one could quite accurately exclude a diagnosis of influenza if the symptom were absent: confined to bed (LR. 0.50), unable to cope with daily activities (LR, 0.39), any systemic symptom (LR, 0.36) and cough (LR, 0.38). Confidence intervals around these point estimates were not given. In the second review, three individual symptoms had LR <0.5, indicating that one could quite accurately exclude a diagnosis of influenza if these were absent [3]: fever ((LR 0.40, 95% CI 0.25–0.66), cough (LR 0.42, 95% CI 0.31–0.57), and nasal congestion (LR 0.49, 95% CI 0.42–0.59).

Two primary studies assessed a combination of symptoms, fever, and cough, in all ages [4] and in persons over 60 years of age [5]. These found positive LRs of 1.9 (95% 1.8–2.1) and 5.9 (95% CI 3.5–6.9) respectively during the winter months, suggesting that if influenza is present in the community the accuracy of a clinical diagnosis of influenza in a patient with fever and cough, especially in an older patient, is likely to be high.

Laboratory diagnosis

Influenza viruses are categorized into three antigenic types, A, B, and C, based on proteins in the nucleocapsid and matrix. Influenza A is further subtyped according to membrane glycoproteins H (hemagglutinin) and N (neuraminidase) [6]. There are 16 known H subtypes and nine N subtypes [6]. Influenza C is an uncommon cause of human infection. Influenza viruses undergo small antigenic changes or "drift" over time which results in yearly epidemics. Major antigenic changes, or "shift" in influenza A virus, with emergence of a new subtype that can be spread from human to human and causes clinically significant disease, result in influenza pandemics associated with worldwide morbidity and mortality, and are not discussed here.

Laboratory tests for the timely diagnosis of influenza are conducted on specimens procured from the respiratory tract obtained from nasal aspirate, swab or wash, or a throat swab or wash, or from serum (Table 12.1). Notably, sputum is not a useful specimen in the diagnosis of influenza and throat swabs are less sensitive than specimens from the nasopharynx. Influenza tests rely on detection of the virus, or the patient's immune response to the virus [7]. As seen in Table 12.1, the types of test available are viral culture, enzyme immunoassay, polymerase chain reaction (PCR), and serology. The usefulness of each test in altering decision-making (e.g., treatment, prophylaxis of contacts, outbreak management) is affected by the timeliness of results. As can be seen, only the respiratory tract specimens are available in a timeline that will be helpful to the clinician.

As with almost all microbiologic tests, accuracy of influenza testing is altered by the time specimens are taken in relation to disease onset and whether specimen procurement is done correctly. Viral shedding tends to be greatest earlier in influenza, and false-negative results may occur when testing is done after 3 days of symptoms since viral replication is decreasing or finished in the normal host. False-negative tests can also occur because of inappropriate specimen handling. False-positive tests are most commonly the result of laboratory error or test characteristics. A full discussion of the test characteristics is beyond the scope of this chapter; the reader is referred to comprehensive reviews which discuss test sensitivity, specificity, and technologic requirements and considerations [7,8].

Radiology

No systematic reviews on the accuracy of diagnosis of influenza-associated lower respiratory tract infection were found. The most commonly used diagnostic imaging test for pneumonia is the chest radiograph [9]. Although imaging can confirm involvement of the lungs, findings are too nonspecific to point to microbiologic etiology. Viral and bacterial pneumonias may have distinguishing features however. The radiologic pattern of viral pneumonia is usually less confluent and homogenous than bacterial pneumonia. The picture in viral infection may be one of air-space nodules (of 4–10 mm), patchy peribronchial ground glass opacity, or air-space consolidation [9]. Hyperinflation is more likely in viral than bacterial pneumonia because of the associated bronchiolitis [9].

Table 12.1 Options for laboratory confirmation of influenza virus infection

Source of specimen	Diagnostic test	Time to test result	Test characteristics
Respiratory tract (NP aspirate, NP swab/wash, throat swab)			
	Rapid antigen detection	<30 minutes	Less sensitive than other respiratory tract tests
	Immunofluorescence microscopy	~1–4 hours	Immunofluorescent antibody detection more sensitive but slower than direct fluorescent antibody detection
	Nucleic acid testing (e.g. RT-PCR)	4–6 hours	Most sensitive and specific tests for influenza
	Virus isolation		
	– by shell vial culture	18–48 hours	Shell vial method more sensitive
	– by conventional culture	3–14 days	
Serum			
	Neutralization test Hemagglutination-inhibition Enzyme immunoassay Complement fixation	Paired serum samples taken during acute and convalescent (2–3 weeks later) phases required	

Adapted from Petric M et al., Role of the laboratory in diagnosis of influenza during seasonal epidemics and potential pandemics [7] and Cox N et al., Manual of Clinical Microbiology [45].
NP, nasopharyngeal; RT-PCR, reverse-transcription polymerase chain reaction.

Treatment

Treatment of influenza includes specific antiviral therapies, alternative therapies, nonspecific supportive measures, and treatment of complications of influenza.

There are two classes of specific antiviral drugs that are available for treatment of influenza and have been shown to alter the natural history of uncomplicated symptomatic infection in randomized controlled blinded trials: M2 ion channel inhibitors (amantadine and rimantidine) and neuraminidase inhibitors (oseltamivir and zanamivir). Amantadine and rimantidine are active against influenza A only and interfere with viral replication by inhibiting the M2 ion channel, which is necessary to acidify the interior of the virus. The neuraminidase inhibitors interfere with the influenza viral enzyme neuraminidase, which cleaves terminal sialic acid from sialic-acid-containing cell surface glycoproteins during replication.

A systematic review of amantadine and/or rimantidine in the therapy of uncomplicated influenza A illness showed reduction in the duration of fever by about 1 day compared to placebo [10], but not a significant reduction in viral shedding from the upper airway. The adverse event profile was similar in placebo and antiviral agent groups [10]. Treatment must be initiated within 48 hours after symptom onset for greatest benefit. The most common adverse effect is central nervous system symptoms such as irritability, insomnia, agitation, and confusion.

Since 2001 an increasing incidence of amantadine- and rimantidine-resistant influenza viruses have been observed [11], leading public health authorities to recommend that this class of drugs not be used for treatment or prophylaxis [12]. Ongoing worldwide surveillance of influenza epidemiology and antiviral resistance will determine if this class of drugs will play a role in influenza management in the future.

Neuraminidase inhibitors prevent the replication of both type A and B influenza viruses by inhibiting influenza virus neuraminidase. Neuraminidase enables release of virions from infected cells by preventing them from self-aggregating and binding to the surface of infected cells. Oseltamivir is a neuraminidase inhibitor that is administered twice daily by mouth, while zanamivir is administered by inhalation.

Two systematic reviews of randomized controlled trials of oseltamivir and zanamivir in the treatment of influenza have shown that both reduce the duration of symptoms by 1 day, and reduce the time before normal activities are resumed by about half a day in healthy adults [13,14]. The most common adverse effect associated with oseltamivir use is gastrointestinal (nausea, vomiting). Zanamivir is not recommended in individuals with underlying airway disease (such as asthma or chronic obstructive pulmonary disease) because of the risk of airway irritation leading to bronchospasm.

A recent systematic review of randomized controlled trials of Chinese medicinal herbs for the treatment of influenza identified two studies with 1012 patients [15]; the evidence was considered insufficient to support or reject use of these products in influenza. Another systematic review of evidence for the effectiveness of a number of complementary therapies also concluded that there was insufficient evidence of therapeutic benefit [16]. A Cochrane review [17] of Oscillococcinum, a homeopathic product derived from duck liver and heart, reduced the length of influenza illness by 0.28 days (95% CI 0.50–0.06).

Supportive care for influenza consists of adequate hydration and symptomatic therapy for discomfort and fever with nonsteroidal inflammatory medications or acetaminophen. Patients who are unable to maintain fluid intake or develop respiratory distress may require care in the hospital setting.

In healthy people influenza is an acute febrile illness that lasts for about 1 week [18]. However, influenza can lead to serious complications including pneumonia (secondary bacterial or primary viral pneumonia) or exacerbation of preexisting lung, cardiac, or other chronic disease [19]. Other complications of influenza virus infection include myositis, encephalitis and other neurologic disorders, pericarditis, and myocarditis. Two recent studies, analyzing large health utilization databases with a combined population of over 80 000, indicate that persons diagnosed with influenza and to whom oseltamivir was prescribed had significant reductions in the risk of pneumonia [20] or respiratory disease [21], otitis media, and hospitalization [20,21]. An observational study of 77 adults admitted for influenza-associated illness found antiviral therapy was associated with a significant reduction in mortality (OR 0.21, 95% CI 0.06–0.80), but was not associated with length of stay [22].

Prognosis

In healthy persons influenza is associated with various combinations of fever, cough, rigors, myalgia, and headache of about 1 week's duration [16] often severe enough to result in workplace absenteeism [23–25]. Complicated influenza can occur in previously healthy persons, but is more likely to occur in persons with certain risk factors. The most striking risk factor for complicated influenza requiring hospital care or influenza-associated death is age. Children under 2 years of age and adults over 65 have admission rates to hospital near 100 per 100 000 age-specific population [26–28].

Certain chronic health conditions, in particular cardiac or pulmonary disease, diabetes and renal failure are associated with higher incidence of hospital admissions than occurs in healthy persons in the same age group [29]. Pregnant women with seasonal influenza are more likely than nonpregnant women to be admitted to hospital in several studies, but do not appear to be at increased risk of adverse fetal outcomes or maternal death [30]. Both age and the presence of the previously mentioned chronic health conditions increase risk of death associated with influenza [12,27,31]. In the US the average annual number of deaths attributable to influenza is 34 000 [12].

Prevention

Three categories of interventions exist for the prevention of influenza: vaccination, infection prevention and control measures, and antiviral drugs.

Immunization is the cornerstone of public health influenza control programs, and in almost all developed countries is recommended on an annual basis for persons at high risk of complicated influenza or of being hospitalized for care of influenza, such as persons over 65 years of age, and those with chronic health conditions such as cardiac or lung disease (Table 12.2). A second important component of influenza immunization is to vaccinate those who care for, or are in regular contact with, persons at high risk of influenza such as household contacts or healthcare providers. This strategy seeks to interrupt spread to vulnerable persons, especially those who cannot be immunized (e.g., children <6 months of age), or are

Table 12.2 Persons for whom annual influenza immunization is recommended because of increased risk of hospitalization, complicated influenza, or death

Children 6–23 months of age
Persons >65 years of age
Persons with immunosuppression, primary or secondary
Persons with chronic pulmonary (including asthma), cardiovascular, renal, metabolic or hematologic disorders
Residents of nursing homes or other chronic care facilities
Pregnant women

less likely to respond to the vaccine (e.g., elderly or immunocompromised people).

Commercial influenza vaccines were first introduced in 1945, and a number of vaccine types are available, namely, injectable inactivated or subunit vaccines, and nasally administered live attenuated products [32]. The strains to be used in each year's vaccine are chosen annually by the World Health Organization based on surveillance data gathered by participating laboratories worldwide.

The efficacy of influenza vaccines in preventing influenza has been evaluated in thousands of patients in randomized controlled clinical trials, and several systematic reviews summarizing these studies are available [1,33–38]. Estimates of influenza vaccine efficacy in a particular season vary according to the degree of match of the circulating strains with the vaccine strain, the age of the recipient and their previous experience with infection or immunization, and the type of influenza vaccine. Two types of outcome measures have been used to assess vaccine efficacy and effectiveness: clinical definitions of respiratory illness, and laboratory-confirmed influenza. Use of the latter more accurate outcome results in higher estimates of vaccine efficacy than does a measure of clinical outcome [1]. A number of different clinical definitions of influenza-like illness have been used, and this will affect the calculation of vaccine efficacy [39,40]. Clinical outcome measures capture non-influenza viral respiratory illness against which influenza vaccine is obviously not effective.

Randomized controlled trials of influenza vaccine demonstrate that influenza vaccine prevents laboratory-confirmed illness in 70–90% of in healthy persons when the circulating strain matches that in the vaccine [1,35]. Estimates of efficacy are lower when there is mismatch, estimated in a recent metaanalysis as 50% (95% CI 27–65) [35]. Randomized controlled trials of inactivated influenza vaccines also show reduction in exacerbations in adults with chronic obstructive pulmonary disease [36] and fewer deaths from pneumonia and overall deaths in elderly residents of nursing homes when their care-givers are immunized [41]. Other reviews have concluded that there is insufficient evidence that influenza immunization reduces asthma exacerbations [33], and that there is no evidence for or against the use of influenza vaccine to reduce pulmonary decline and respiratory exacerbations in patients with bronchiectasis [34].

Antiviral drugs have also been approved for the prevention of seasonal influenza as well as for treatment of established illness. Chemoprophylaxis can be considered in the following circumstances: to prevent infection in institutional settings (e.g., long-term care facility or hospital) once influenza is identified in the community or in the facility, or as post-exposure prophylaxis for high-risk persons in whom vaccine has not or cannot be administered or is not expected to be efficacious (e.g., immunocompromised people). Studies done prior to widespread adamantine resistance showed amantadine and rimantidine were effective in prevention of influenza A (60–70% reduction) [10] including in elderly persons [42]. This class of drugs is not recommended for prophylaxis at the time of writing because of high levels of resistance worldwide [43].

The neuraminidase inhibitors are effective in prevention of influenza subtypes A and B, and have been used as seasonal proprophylaxis (e.g. for 6 to 8 weeks when influenza is in the community) or as a post-exposure measure in household or other close contacts. Two metaanalyses had similar findings: one group found a relative reduction of 70–90% in the odds of developing influenza [14], and a second found an efficacy of 58–89% in healthy adults depending on the strategy of prophylaxis [13].

Infection prevention and control measures consist of behaviors and use of personal protective equipment that will interrupt transmission of influenza virus from infected persons or influenza-contaminated articles to susceptible persons. Influenza virus is transmitted predominately through droplets from the respiratory tract which are expelled during coughing or sneezing, or transmitted during direct contact [44]. Hand hygiene using soap or antimicrobial agents

(e.g., waterless handrubs, antimicrobial soap) is effective at eliminating virus from the hands. In addition to Standard Precautions, transmission-based Precautions are recommended for the care of a hospitalized patient with influenza. Placement in a single room is preferred and a standard surgical mask should be worn within 3 feet of the patient [45].

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CHAPTER 13
Critical care

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Infection represents a major source of morbidity and mortality in the intensive care unit (ICU). Whether infection is the principal cause of critical illness or a secondary complication, the prevention, surveillance, diagnosis, and treatment of infection in the ICU pose unique challenges and require vigilant care.

Case presentation

Mr KW is a 56-year-old obese male presenting to the emergency room feeling unwell. Three weeks ago he underwent an umbilical hernia repair including mesh placement. He now has fever, abdominal pain, and lightheadedness. His temperature is 39.4°Celsius. His heart rate is 128 bpm, supine blood pressure 88/60 mmHg, and respiratory rate 34 bpm. His abdominal incision is healed and nontender. His leukocyte count is 34 with toxic granulation. His chest radiograph shows patchy airspace disease, and a CT scan reveals an infected mesh.

Sepsis

Epidemiology

In the United States, the incidence of severe sepsis is estimated at 751 000 cases per year, with 2.26 cases for every 100 hospital discharges [1]. Estimates of the hospital mortality rate of sepsis range from 20% to 60% [2]. While hospital mortality rates from sepsis are declining in the US [3], survivors face an increased risk of death from nonseptic causes for up to 5 years [4].

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Definitions

The pathophysiology of sepsis involves an uncontrolled inflammatory response. An initial hyperimmune state generally precedes immunosuppression [5]. Hemodynamic instability and dysregulation of coagulation and fibrinolysis are key contributors to tissue hypoxia and vital organ injury [6]. Multiple organ failure is a hallmark of severe sepsis and the most common cause of death.

In 1992, the American College of Chest Physicians and the Society of Critical Care Medicine published definitions of sepsis-related syndromes [7]. The cornerstone of these definitions was the systemic inflammatory response syndrome (SIRS), characterized by two or more of: hyper- or hypothermia, tachycardia, tachypnea, leukocytosis or leucopenia. Notably, SIRS may be precipitated by nonseptic events, including trauma, burn injury, and pancreatitis; therefore, the diagnosis of sepsis requires both SIRS and a confirmed or presumed source of infection. Severe sepsis refers to sepsis complicated by at least one major organ dysfunction. Septic shock includes persistent hypotension that is unresponsive to fluid resuscitation.

Revisions to these definitions in 2001 recognize alternative manifestations of SIRS including laboratory markers of inflammation, organ dysfunction, and other evidence of tissue hypoperfusion (Table 13.1) [8]. The revised criteria allow more room for clinical judgment, since missing the diagnosis can have catastrophic consequences.

Management

Management of the septic patient involves a multifaceted approach directed against the complex underlying pathophysiology. Early goal-directed resuscitation and prompt administration of antibiotics are crucial.

Table 13.1 Diagnostic criteria for sepsis

Infection,[a] documented or suspected, and some of the following:[b]
General variables
Fever (core temperature >38.3°C)
Hypothermia (core temperature <36°C)
Heart rate >90 min^{-1} or >2 SD above the normal value for age
Tachypnea
Altered mental status
Significant edema or positive fluid balance (>20 mL/kg over 24 h)
Hyperglycemia (plasma glucose >120 mg/dL or 7.7 mmol/L) in the absence of diabetes
Inflammatory variables
Leukocytosis (WBC count >12 000 μL^{-1})
Leukopenia (WBC count <4000 μL^{-1})
Normal WBC count with >10% immature forms
Plasma C-reactive protein >2 SD above the normal value
Plasma procalcitonin >2 SD above the normal value
Hemodynamic variables
Arterial hypotension[b] (SBP <90 mmHg, MAP <70, or an SBP decrease >40 mmHg in adults or <2 SD below normal for age)
SvO_2 >70%[b]
Cardiac index >3.5 L min^{-1} M^- [23] [WU1]
Organ dysfunction variables
Arterial hypoxemia (PaO_2/FIO_2 <300)
Acute oliguria (urine output <0.5 mL kg^{-1} h^{-1} or 45 mmol/L for at least 2 h)
Creatinine increase >0.5 mg/dL
Coagulation abnormalities (INR >1.5 or aPTT >60 s)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count <100 000 μL^{-1})
Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 mmol/L)
Tissue perfusion variables
Hyperlactatemia (>1 mmol/L)
Decreased capillary refill or mottling

WBC, white blood cell; SBP, systolic blood pressure; MAP, mean arterial blood pressure; SvO_2, mixed venous oxygen saturation; INR, international normalized ratio; aPTT, activated partial thromboplastin time.

[a]Infection defined as a pathologic process induced by a microorganism.

[b]SvO_2 sat >70% is normal in children (normally, 75–80%), and cardiac index 3.5–5.5 is normal in children; therefore, NEITHER should be used as signs of sepsis in newborns or children

Diagnostic criteria for sepsis in the pediatric population are signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature >38.5°C or <35°C), tachycardia (may be absent in hypothermic patients), and at least one of the following indications of altered organ function: altered mental status, hypoxemia, increased serum lactate level, or bounding pulses.

Source: Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. Crit Care Med 2003;31:1250–6.

Thereafter, consideration of source control, activated protein C, and systemic corticosteroid therapy may be life-saving.

Early goal-directed therapy

The aim of goal-directed therapy in sepsis is the correction of hemodynamic disturbances that contribute to tissue hypoxia. Historically, goal-directed therapy referred to specific interventions aimed to achieve supraphysiologic values of cardiac index and oxygen delivery. A landmark trial of 762 septic patients showed no improvement in morbidity or mortality with this approach [9], and a later systematic review reinforced this finding [10]. However, the experimental interventions in these trials were generally initiated up to 48 hours after ICU admission.

Current evidence suggests that goal-directed resuscitation should be initiated earlier, before the onset of irreversible tissue damage, and should include more conservative physiologic goals. A recent innovative trial randomly allocated 263 septic patients, at the time of presentation to the emergency department, to 6 hours

of early goal-directed therapy versus standard care prior to ICU admission [11]. The experimental intervention involved an iterative assessment of hemodynamic parameters with specific actions targeted to precise physiologic goals. First was the infusion of 500 mL of crystalloid solution every 30 minutes until central venous pressure (CVP) measurements ranged from 8 to 12 mmHg. At that point, vasopressor administration targeted a mean arterial pressure (MAP) of at least 65 mmHg. Thereafter, if central venous oxygen saturation was less than 70%, red blood cells were transfused to achieve a hematocrit of at least 30%. If central venous oxygen saturation remained below 70%, dobutamine was administered to achieve that goal. Antibiotics were given at the discretion of the treating physicians, and there were no significant differences between groups in terms of time to antibiotic administration or adequacy of antimicrobial coverage. With this multifaceted intervention, 28-day mortality rates decreased from 46.5% to 30.5%, corresponding to a relative risk of 0.58 ($P = 0.009$) and a number-needed-to-treat of 6. Early goal-directed therapy also reduced the duration of vasopressor therapy, mechanical ventilation, and hospital stay.

These findings popularized the notion that optimal sepsis management begins upon presentation to the emergency room. A subsequent synthesis of before-and-after studies evaluating comparable protocols for early goal-directed therapy in sepsis found a similar overall relative mortality risk of 0.54 [12]. Notwithstanding the selection bias and confounding factors that typically complicate before-and-after studies, this finding supported the feasibility of early goal-directed therapy in emergency departments and elsewhere in the hospital. Current guidelines, therefore, recommend early resuscitative efforts at the time of presentation, targeting a CVP of 8 to 12 mmHg, MAP not less than 65 mmHg, urine output exceeding 0.5 mL/kg/hour, and central or mixed venous oxygen saturation of at least 70% [13].

Antimicrobial therapy

Another pillar of sepsis management is the prompt administration of appropriate antimicrobial therapy. The importance of early antimicrobials was highlighted by a 5-year retrospective study of 2700 patients with septic shock [14]. Among patients who received antimicrobial therapy that was adequate to treat subsequently identified pathogens, delays in antimicrobial therapy clearly correlated with mortality

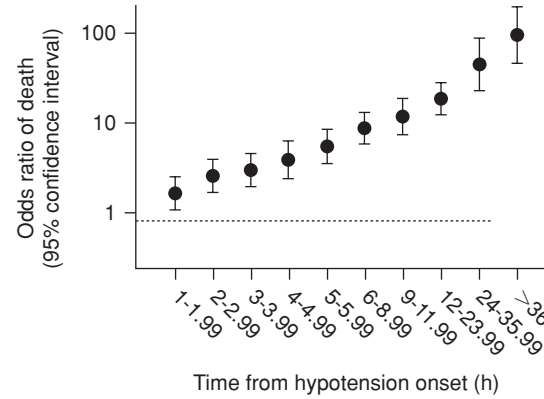

Figure 13.1 Mortality risk (expressed as adjusted odds ratio of death) with increasing delays in initiation of effective antimicrobial therapy. Bars represent 95% confidence interval. An increased risk of death is already present by the second hour after hypotension onset (compared with the first hour after hypotension). The risk of death continues to climb, though, to > 36 h after hypotension onset. Reproduced from reference [14]: Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006;34:1589–96.

(Fig. 13.1). Patients receiving appropriate coverage within the first hour of hypotension had a survival rate of 79.9%, and survival decreased by approximately 8% for each hour of delay.

The choice of empiric antimicrobial therapy is paramount. Among 655 critically ill patients with sepsis who ultimately had positive culture results, hospital mortality when initial antimicrobial therapy was inadequate to treat the pathogen was 52.1%, far exceeding the 12.2% mortality rate among patients receiving adequate antimicrobial therapy [15]. Regression modeling determined that inadequate antimicrobial treatment was the strongest determinant of hospital mortality, with an adjusted odds ratio of 4.27. Other studies reported similar findings [16,17].

Initial antimicrobial therapy depends on the presumed source of infection. Empiric therapy should cover any pathogens commonly associated with the particular infection, including resistant organisms for patients with known risk factors. An evidence-based review determined that acceptable empiric regimens in septic patients with an unclear source include a β-lactam in combination with an aminoglycoside, or monotherapy with a third- or fourth-generation cephalosporin, carbapenem, or extended-spectrum

carboxypenicillin or, alternatively, ureidopenicillin with a β-lactamase inhibitor [18]. With the increasing prevalence of community-acquired MRSA, consideration may also be given to adding an antibiotic to cover MRSA based on local resistance patterns and clinical suspicion. Prompt administration of broad-spectrum empiric agents is followed by culture-directed tailoring of therapy as soon as possible [19].

Source control

A persisting collection of microorganisms will continue to trigger the inflammatory response of sepsis [20]. When a source of infection cannot be eradicated solely with antibiotics, one must consider source control [13,20]. Percutaneous or surgical drainage is indicated for infection within a closed space, including abscess, empyema, or cholangitis. Debridement involves the removal of infected or necrotic tissue, either surgically, with irrigation, or using wet-to-dry dressings. Device removal is important in patients with an infected foreign body, such as a central venous catheter, urinary catheter, or prosthetic joint. Other definitive source control measures include amputation of a gangrenous limb and resection of ischemic bowel.

Activated protein C

Among a host of immunomodulatory therapies proposed for the management of sepsis, drotrecogin alpha (activated), a recombinant human form of activated protein C (rhAPC), is currently the treatment with the strongest evidence for survival benefit.

Activated protein C is a naturally occurring inhibitor of both thrombosis and inflammation. The potential efficacy of rhAPC for severe sepsis was demonstrated in the original PROWESS trial where nearly 1700 patients with severe sepsis received either rhAPC or placebo infusion for 96 hours [21]. With rhAPC therapy, 28-day mortality fell from 30.8% to 24.7%, signifying a relative risk of 0.80 ($P = 0.005$). Patients receiving rhAPC, however, had a significantly higher rate of major bleeding events (3.5% versus 2.0%), and these occurred even more frequently (6.5%) in a subsequent open-label, single-arm study of over 2400 patients [22]. The open-label study also observed a significantly lower mortality rate among patients who received rhAPC within the first 24 hours of organ dysfunction (22.9% versus 27.4%).

Initial enthusiasm for rhAPC therapy in sepsis [13] has been tempered by less striking results of later trials in pediatrics [23] and in lower-risk [24], critically ill adults [25]. An additional trial is under way to clarify the role for early administration of rhAPC to patients who are most likely to respond. Meanwhile, current guidelines include a weak recommendation to administer rhAPC to patients with severe sepsis and APACHE II score greater than 25. Contraindications include active internal bleeding, hemorrhagic stroke within 3 months, neurosurgery or head trauma within 2 months, trauma with an increased risk of significant bleeding, epidural catheter, or intracranial mass lesion [13].

Corticosteroid therapy

The role for systemic corticosteroids in the management of sepsis is equally controversial. Known for their anti-inflammatory properties, steroid therapy did not live up to initial expectations: two metaanalyses including trials from 1966 to 1993 showed no evidence of a survival benefit [26,27]. However, early practice was to use short courses of high-dose corticosteroids. Current evidence suggests that sepsis is frequently complicated by adrenal insufficiency and glucocorticoid resistance [28]; therefore, longer treatment using smaller, physiologic doses of corticosteroids may be more appropriate. In a more recent systematic review [29], a subgroup analysis of five trials administering longer courses of low-dose corticosteroids ($\geqslant$300 mg/day hydrocortisone or equivalent for at least 5 days) found a significant reduction in the relative risk of mortality at 0.80. Moreover, there was no apparent increase in the rate of adverse events.

A newly published trial was designed to retest the role for low-dose steroids in sepsis [30]. The largest trial to date, CORTICUS stopped early and was underpowered to detect a mortality effect. Of note, there was no apparent survival benefit even among patients found to be adrenally insufficient on corticotropin stimulation. Steroid therapy was associated with a shorter time to shock reversal; however, there was also an increased risk of complications. Since earlier trials had reasonably comparable methods, populations and therapeutic protocols, an update to the metaanalysis is prudent and will likely show a nonstatistically significant mortality reduction. For

now, whether steroids benefit any critically ill septic patients remains uncertain. Refraining from steroid use altogether, administering only to the most ill, and administering to a wider group of septic patients all remain justifiable courses of action.

Case presentation (continued)

In the ER, Mr KW promptly receives intravenous piperacillin-tazobactam and the mesh is surgically removed that day. Postoperatively, he is transferred to the intensive care unit on vasopressors. His leukocyte count is 36, his lactate level 3.5. His chest radiograph reveals diffuse airspace disease.

Upon ICU admission, 2 L of intravenous crystalloid bring Mr KW's central venous pressure to 12 cmH_2O and his central venous oxygen saturation, measured through a right subclavian catheter, to 72%. He continues to require vasopressor support. Fluid collected during surgery shows gram-negative bacilli, as do two blood cultures. Later, *E. coli* sensitive to cephazolin is identified from all three cultures. The clinical team discontinues piperacillin-tazobactam and initiates cephazolin therapy. While his acute lung injury progresses, his blood pressure improves over 6 hours, though still requiring vasopressor support. With results from an ACTH stimulation test pending, Mr KW receives neither corticosteroid therapy nor rhAPC.

Later, off vasopressors and with his lung injury slowly resolving, Mr KW develops signs of a new infection: fever, tachycardia, increased respiratory rate, and recurrent leukocytosis with band cells.

Ventilator-associated pneumonia

Epidemiology

Ventilator-associated pneumonia (VAP) refers to pneumonia arising more than 48 hours after endotracheal intubation [31]. Incidence and mortality estimates vary depending on the population, diagnostic techniques, and other variables. A study of over 9000 ICU patients in the US found that VAP occurred in 9.3% [32]. Although the investigators detected no increase in mortality attributed to VAP, patients with VAP had prolonged mechanical ventilation, ICU stay, and hospitalization. Moreover, the mean excess hospital costs attributable to each case of VAP exceeded $40 000. A related study of patients in Canadian ICUs reported similar findings, with a trend towards higher mortality among patients with VAP (23.7% vs 17.9%), and ICU stays that were prolonged by an average of 4.3 days [33].

Pathophysiology and microbiology

Two main factors contribute to the development of VAP: bacterial colonization of the upper airways and aspiration [34,35]. Critically ill patients become colonized with a variety of organisms originating from their own gastrointestinal tract and from the hospital environment. This process is facilitated by patients' inability to clear their secretions and by numerous catheters that breach the skin and mucosal barriers. Colonizing bacteria infect the lower airways via aspiration of secretions from the upper respiratory tract.

The microbiology of VAP differs from community-acquired pneumonia, with gram-negative and drug-resistant organisms accounting for a significant proportion of cases. Gram-negative bacilli, including *Pseudomonas aeruginosa* and *Enterobacter* species, tend to be the most common organisms isolated. Gram-positive cocci are also a frequent cause, predominantly *Staphylococcus aureus*. Surveillance data from one American hospital revealed that 59% of VAP cases were caused by gram-negative bacilli, most commonly *P. aeruginosa*, *Stenotrophomonas maltophilia*, and *Acinetobacter* species. The most common gram-positive organism causing VAP was methicillin-resistant *S. aureus* (MRSA) [36]. Another American study similarly found that *P. aeruginosa* and *S. aureus* were the most common pathogens identified in the setting of VAP [37].

Prevention

Understandably, a great deal of research has focused on VAP prevention. Several preventive strategies are supported by current research evidence, including oral intubation, endotracheal tube care, patient positioning, oropharyngeal decontamination, and stress ulcer prophylaxis [35,38].

For patients requiring intubation, the oral route is preferred over the nasal route, which is associated with an increased incidence of maxillary sinusitis [39]. Sinusitis is associated with the development of VAP, presumably secondary to aspiration of infected

nasal secretions into the lungs [35]. In a trial of 300 ICU patients randomized to either oral or nasal intubation, there were trends towards less sinusitis and pneumonia with orotracheal intubation [40].

Maintenance of the endotracheal tube can affect the incidence of VAP. Persistent endotracheal cuff pressures less than 20 cmH_2O may increase the risk of VAP [41]. In addition, three trials have shown that aspiration of subglottic secretions can significantly reduce the incidence of VAP [42–44]. Both of these interventions help to prevent aspiration of secretions around the endotracheal tube and into the lungs. Interventions that appear to have no effect on the incidence of VAP include frequent changes of the ventilator circuit, suction catheter, or humidifier, and use of a closed suction system [35,38].

Patient positioning is another important consideration in VAP prevention. Nursing in the supine position facilitates aspiration of potentially infected secretions that lead to VAP [45]. A randomized trial to test this hypothesis stopped early after an interim analysis demonstrated a significantly reduced rate of VAP in patients nursed in a semirecumbent position compared to those who were supine (8% vs 34%, relative risk 0.24) [46].

Oropharyngeal decontamination may prevent VAP by reducing the amount of infected secretions in the oropharynx. A metaanalysis of eleven randomized trials found a statistically significant reduction in VAP rates with chlorhexidine mouthwash compared to placebo or standard care (relative risk 0.56; 95% CI 0.39–0.81), and a trend toward VAP reduction with oral decontamination using antibiotic agents [47]. This study did not detect an effect on mortality or duration of ICU stay.

The relationship between stress ulcer prophylaxis and VAP is controversial. Patients receiving mechanical ventilation and those with coagulopathy carry increased risk of gastrointestinal bleeding, and pharmacologic measures to reduce gastric acidity can reduce bleeding rates [48]. However, reducing gastric acidity also facilitates microbial colonization of the aerodigestive tract [45]. A multicentre trial that randomized 1200 mechanically ventilated patients to either ranitidine or sucralfate therapy found a lower rate of bleeding with ranitidine (RR 0.44, 95% CI 0.21–0.92), with no significant effect on VAP incidence. A subsequent metaanalysis confirmed that rates of pneumonia were similar between ranitidine and sucralfate, but also found that neither agent was significantly associated with increased pneumonia compared to placebo, and furthermore, neither differed from placebo with respect to bleeding rates [49]. After weighing all of the evidence, current guidelines recommend reserving stress ulcer prophylaxis for patients at high risk of gastrointestinal bleeding, and using histamine-receptor antagonists rather than sucralfate [35,38].

Diagnosis

The diagnosis of VAP presents unique challenges. Clinical manifestations typically consist of new or progressive infiltrates on chest radiography with purulent tracheal secretions, fever, and leukocytosis. However, a variety of alternative pathologies, alone or in combination, can lead to a similar constellation of findings, including acute lung injury, atelectasis, congestive heart failure, and nonpulmonary infections [50]. A study of 84 ICU patients with new infiltrates and purulent secretions demonstrated the limited utility of clinical features in the diagnosis of VAP [51]. A team of physicians predicted whether or not the patients had pneumonia based on all available clinical information, and the actual diagnosis was made based on histopathology, pleural fluid culture, or computed tomography criteria. Only 62% of patients with confirmed VAP were correctly diagnosed, as were 84% of patients without pneumonia.

The clinical pulmonary infection score (CPIS) was developed to improve the clinical diagnosis of VAP. The CPIS is a score of 0 to 12 based on temperature, leukocyte count, tracheal secretions, oxygenation, chest radiography, and microbiology findings, with scores greater than 6 suggestive of VAP [52]. A management strategy based on the CPIS was studied in 81 ICU patients with new pulmonary infiltrates [53]. Patients with a score of less than or equal to 6, who were considered to be at low likelihood of having VAP, were randomized to receive either standard VAP treatment or an experimental intervention that consisted of 3 days of antibiotic therapy followed by reevaluation of CPIS, at which time antibiotics would be discontinued if CPIS was still less than or equal to 6. The study found no difference between the two groups with respect to mortality or duration of ICU stay, though the experimental group had significantly lower rates of antimicrobial usage, antibiotic-resistant organisms, and superinfections. This suggested that the CPIS-based strategy may be a safe and cost-effective approach to the diagnosis and management

of VAP. However, a subsequent study evaluating a modified version of the CPIS found that scores did not differ significantly between patients with and without confirmed pneumonia [54].

Since clinical criteria alone are insufficiently accurate to diagnose VAP, airway sampling for Gram stain and culture is often used to confirm the diagnosis. Samples may be obtained via endotracheal aspirate or, alternatively, during bronchoscopy using either a protected specimen brush (PSB) or bronchoalveolar lavage (BAL). Cultures with greater than 1000 colony-forming units (CFU)/mL from PSB sample or greater than 10 000 CFU/mL for BAL specimens are generally considered diagnostic of VAP [55]. Both PSB and BAL samples for diagnosing VAP have been validated against postmortem lung examination [56]. On the other hand, bronchoscopy is an invasive and resource-intensive diagnostic technique, so many clinicians rely upon endotracheal aspiration. The utility of tracheal aspirates is limited by low specificity because the upper airways of ventilated patients are frequently colonized with bacteria that may not be infecting the lower airways [55].

Invasive and noninvasive diagnostic approaches have been compared, and a metaanalysis of randomized trials found significant heterogeneity among studies [57]. Overall there was no difference in mortality between the two techniques, although antibiotics were more likely to be changed among patients randomized to invasive diagnosis. A trial randomly assigning 740 patients with suspected VAP to undergo either BAL or endotracheal aspiration found no effect on mortality, duration of ICU or hospital stay, duration of mechanical ventilation, or antibiotic use [58]. Given that invasive diagnostic techniques have not been shown to improve clinical outcomes, noninvasive tracheal aspiration is an accepted method of airway sampling in patients with suspected VAP.

Management

Patients with suspected VAP require empiric antibiotic therapy to cover potential pathogens while awaiting the results of microbiologic testing. The initial choice of antibiotics will depend on the degree of risk of colonization with multidrug-resistant (MDR) organisms. Risk factors include duration of hospitalization 5 or more days, antimicrobial therapy within preceding 3 months, hospitalization within preceding 3 months, residence in a nursing home or other long-term care facility, chronic dialysis, receiving home care for wounds or any intravenous therapy, immunosuppression, high rates of antibiotic resistance in the community or hospital, and household members known to have a MDR pathogen [31].

Patients with early-onset VAP (occurring in the first 4 days of hospitalization), in the absence of other risk factors, are more likely to have pneumonia caused by methicillin-sensitive *S. aureus* and antibiotic-sensitive *Enterobacteriaceae* [59]. Treatment options include a third-generation cephalosporin or a respiratory fluoroquinolone. Patients with late-onset VAP or other risk factors for MDR pathogens require combination therapy to cover MRSA and potentially drug-resistant gram-negative bacilli, in addition to the usual pathogens.

Prompt initiation of empiric antibiotic therapy is important. A study of 107 ICU patients with suspected VAP determined that a delay of greater than 24 hours was an independent risk factor for hospital mortality, with an adjusted odds ratio of 7.68 (95% CI 4.50–13.09, $P < 0.001$) [60]. The duration of antibiotic therapy can often be limited to 8 days based on the results of a multicenter trial of 401 ICU patients with VAP [61]. These patients were randomized to either 8-day or 15-day courses of antibiotics, and there was no significant mortality difference between the two groups. However, patients with pneumonia caused by nonfermenting gram-negative bacilli, including *P. aeruginosa*, were more likely to experience a relapse of their infection when treated for only 8 days and thus may require more prolonged therapy.

Case presentation (continued)

Investigating for a nosocomial infection, the clinical team performs a bronchoscopy (because there are scant secretions on endotracheal aspiration), a urine analysis (which is negative and not sent on for culture), and paired quantitative blood cultures. They remove the subclavian catheter that Mr KW no longer requires. Tenacious secretions are detected on bronchoscopy, and the chest radiograph shows a subtle new opacification in the right middle lobe; Mr KW is started empirically on piperacillin-tazobactam. However, 4 days later, with resolution of his fever and leukocytosis, no organisms cultured and persistent subtle opacification of the right middle lobe, empiric antibiotics are discontinued.

Catheter-related bloodstream infections

Epidemiology

ICU patients require various intravascular catheters for monitoring and treatment purposes, and catheter-related bloodstream infections (CRBSI) are one of the potential complications. Rates of CRBSI differ depending on the type of catheter and site of insertion [62]; however, a nationwide surveillance study in the US determined the overall incidence of CRBSI related to central venous catheters (CVCs) among ICU patients was 4% [63]. Estimates of the attributable mortality of CRBSI in ICU patients range from zero to 40%, but these studies consistently observed increased duration of ICU and hospital stay [64,65]. The mean excess costs associated with each CRBSI are estimated at US$30 000–40 000 [65,66].

Etiology

The pathogenesis of CRBSI involves bacterial colonization of the CVC, both in biofilms and in free forms [66]. Virtually all intravascular catheters become colonized, but the likelihood of developing a CRBSI is related to bacterial load, surface properties of the catheter, and host immunity. Colonizing organisms commonly originate from the skin and migrate along the extraluminal surface of the catheter into the bloodstream. Organisms may also enter the bloodstream intraluminally through the catheter hub, often via the hands of healthcare workers.

National surveillance in the US found the most common pathogens in CRBSI are coagulase-negative *Staphylococci* (35.9%), *S. aureus* (16.8%), *Candida* species (10.1%), and *Enterococcus* species (9.8%). These are followed by *P. aeruginosa* (4.7%) and other gram-negative bacilli [67].

Prevention

The risk of CRBSI is minimized with careful attention to the insertion site and technique, catheter care, and duration of use.

The site of catheter insertion is a significant determinant of infection risk. A prospective observational study of over 2000 patients found that the incidence rates of CRBSIs for subclavian, internal jugular, and femoral catheters were 0.97, 2.99, and 8.34 per 1000 catheter-days, respectively [68]. Increased infection risk with femoral catheters was confirmed in a trial of 289 ICU patients randomly assigned to femoral versus subclavian central venous catheterization [69]. Accordingly, current guidelines recommend avoiding femoral catheters and choosing the subclavian site whenever possible [70].

Use of sterile technique and full barrier precautions, including cap, mask, sterile gown and gloves, and large drape can reduce the risk of a CRBSI [70]. A randomized trial of 176 patients comparing maximum barrier precautions to limited barrier precautions with only sterile gowns and small drape observed significantly fewer CRBSIs with maximum barrier precautions (2.4% vs 7.2%, $P = 0.03$), and a nonsignificant reduction in the rate of sepsis [71].

Maintenance of the central catheter is another important consideration in preventing infection. Skin disinfection at the insertion site can reduce bacterial colonization of the skin. A metaanalysis of studies comparing chlorhexidine and povidone-iodine for catheter site care demonstrated a relative risk of 0.49 (95% CI 0.28–0.88) for CRBSI among patients treated with chlorhexidine-based solutions (Fig. 13.2) [72]. Catheter hubs should be cleaned with antiseptic prior to accessing the ports in order to reduce the risk of introducing microbes directly into the catheter lumen. Solutions containing 70% ethanol were more effective than chlorhexidine at reducing bacterial contamination of catheter hubs [73]. Finally, proper hand hygiene should be observed prior to catheter use or site care [70].

The risk of CRBSI increases over time, but prophylactic replacement of central venous catheters has not been found to reduce infection risk [74]. A systematic review of six trials comparing routine catheter changes (after 3 or 7 days) with catheter replacement on an "as needed" basis found no difference in CRBSI rates [75].

A multifaceted intervention to reduce CRBSI was evaluated in over 100 ICUs in the US [76]. The intervention consisted of five components: hand washing prior to any handling of the catheter, full barrier precautions during insertion, chlorhexidine for routine skin disinfection, avoidance of femoral catheterization whenever possible, and removal of unnecessary catheters. Measurement of CRBSI at baseline and at regular intervals for up to 18 months after implementation of the multifaceted intervention revealed a reduction in the mean infection rate from 7.7 per 1000 catheterays at baseline to 1.4 per 1000 catheter-days during the

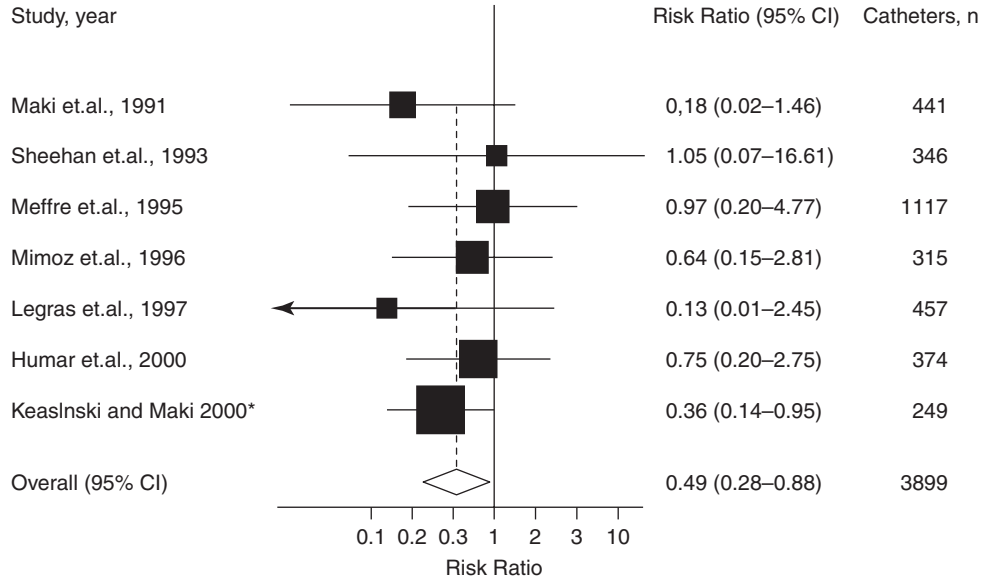

Figure 13.2 Analysis of catheter-related bloodstream infection in studies comparing chlorhexidine gluconate and povidone-iodine solutions for care of vascular catheter sites. The diamond indicates the summary risk ratio and 95% CI. Studies are ordered chronologically. The size of squares is proportional to the reciprocal of the variance of the studies. For the test for heterogeneity of treatment effect, $P > 0.2$. Reproduced from reference [72]: Chalyakunapruk N, Veenstra DL, Lipsky BA, Saint S. Chlorhexidine compared with povidone-iodine solution for vascular catheter-site care: a meta-analysis. Ann Intern Med 2002;136:792–801.

period of follow-up. This demonstrates that relatively simple measures can have a significant and prolonged effect on the prevention of CRBSI.

Diagnosis

The diagnosis of a primary bloodstream infection requires at least one of the following criteria: isolation of a pathogen from one or more blood cultures (not related to infection at any other site); isolation of a common skin contaminant from two or more blood cultures drawn on separate occasions with at least one systemic manifestation of infection (fever, chills, hypotension) and no other suspected source of infection; or a positive antigen test (e.g., *Streptococcus pneumoniae*, group B streptococcus, *Haemophilus influenzae*, or *Neisseria meningitides*) in the setting of systemic manifestation of infection, with no other apparent source. CRBSI is present if a patient with a primary bloodstream infection has had a central venous catheter in use during the 48 hours prior to the onset of infection [70].

Most patients with CRBSI develop a fever and they may have other features of SIRS. However, these findings are not specific for CRBSI [77]. Further, prospective evaluation suggests that signs of inflammation at the catheter insertion site, including pain, swelling, erythema, and purulence, are present in only 10% of patients with CRBSI. These features have high specificity (94 to 99%) but low sensitivity (0 to 3%) [78].

Clinical features suggestive of infection in a patient with an intravascular catheter should prompt further microbiologic evaluation. Two samples of blood should be cultured with at least one taken from a peripheral venipuncture site [77]. Positive blood cultures drawn from a CVC can be difficult to interpret because they may represent catheter colonization rather than bloodstream infection. A retrospective study of 271 ICU patients compared the utility of blood cultures drawn from central venous catheters and peripheral venipuncture [79]. Negative predictive values were similar (97% and 95%, respectively); however, positive predictive values were higher for peripheral samples (82%) than central catheters (61%), and the difference was statistically significant. Therefore a positive culture from a peripheral sample is helpful in differentiating true CRBSI from colonization of a central venous catheter.

Once bacteremia is established, or whenever a CRBSI is suspected, several techniques may help to

determine whether an intravascular catheter is the source. One option is to remove the catheter and to culture it either semiquantitatively or quantitatively. The disadvantage of this approach is that it may lead to unnecessary removal of catheters [77].

Alternative diagnostic approaches include "paired quantitative blood cultures" and "differential time to positivity" [80]. The principle behind both methods is that the bacterial load will be inversely proportional to the distance from an infected catheter. The first technique involves obtaining two quantitative blood cultures drawn simultaneously from the central venous catheter and a peripheral vein. A five times greater colony count from the CVC than the peripheral sample is considered diagnostic of CRBSI. The second technique involves comparing the time it takes for each sample to become positive. A diagnosis of CRBSI is established if the culture from the CVC becomes positive at least 2 hours before the peripheral sample.

A metaanalysis of 51 studies compared the diagnostic properties of qualitative, semiquantitative, and quantitative catheter cultures, qualitative and quantitative catheter-drawn cultures, paired quantitative cultures, differential time to positivity, and a rapid diagnostic test called acridine orange leukocyte cytospin [81]. Paired quantitative blood culture was most accurate, with an overall sensitivity of 89% and specificity of 98%.

Case presentation (continued)

Among the investigations for nosocomial infection, the blood culture from Mr KW's central venous catheter identified coagulase-negative staphylococci and the peripheral blood culture was negative, consistent with contamination of the central catheter specimen or colonization of the catheter itself.

Management

Management of suspected CRBSI includes antimicrobial therapy and consideration of catheter removal. Vancomycin is a common choice for empiric therapy that will cover the most common pathogens, coagulase-negative staphylococci and *S. aureus*. Empiric gram-negative and *P. aeruginosa* coverage may be prudent if the patient is demonstrating signs of sepsis. Prompt catheter removal is indicated if the patient is septic or has signs of infection at the insertion site [77].

Identification of the causative organism will guide subsequent management. For coagulase-negative staphylococcal infection, immediate catheter removal is not essential for all patients, particularly those with difficult venous access or those who will require central access for a short period of time. A retrospective study of 70 patients with catheter-related coagulase-negative staphylococcal infection found recurrence in 20% of patients with retained catheters versus 3% of patients whose catheters were removed ($P < 0.05$) [82]. Vancomycin therapy is indicated for 5–7 days if the catheter is removed, versus 10–14 days if the catheter remains in place [77].

CRBSI caused by *S. aureus* requires removal of the catheter; failure to do so significantly increases the risk for infection recurrence and mortality [83]. *S. aureus* bacteremia is also commonly associated with metastatic infections, including infective endocarditis; therefore, transesophageal echocardiography (TEE) should be considered to identify cases of *S. aureus* endocarditis, which requires prolonged antibiotic therapy [77,84]. If the *S. aureus* is susceptible, β-lactam antibiotics or a first-generation cephalosporin are appropriate as first-line therapy. The recommended duration of therapy for patients with no evidence of infective endocarditis is 14 days [77].

CRBSI due to gram-negative bacilli are less common, but a small retrospective study found that catheter removal significantly reduced the likelihood of recurrence (odds ratio 0.13, 95% CI 0.02–0.75) [85]. Catheter removal is followed by a 14-day course of antibiotic therapy [77].

Catheter removal is also essential in CRBSI caused by *Candida* species. A prospective study of 145 patients with catheter-related candidemia found that failure to remove the catheter was significantly associated with mortality (OR 4.81) [86]. Options for empiric antifungal therapy include amphotericin B, an echinocandin, or fluconazole; the choice may depend upon the local incidence of fluconazole-resistant *C. glabrata* and *C. krusei* [80]. Blood cultures should be repeated routinely, and the recommended duration of treatment is 14 days after the last positive blood culture [87].

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PART 2
Special populations

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CHAPTER 14
Infection control

Graham M. Snyder, Eli N. Perencevich & Anthony D. Harris

Surgical site infections

Case presentation 1

A new chief of surgery, who happens to be a cardiothoracic surgeon, arrives at your hospital. She calls you and says that she is concerned that the risk-adjusted surgical site infection rates at her new hospital might be higher than the rates at her previous hospital. She wants to set up a meeting with you to discuss ways to minimize the risk of surgical site infection in her patients.

Burden of illness, cost, and relevance to clinical practice

Surgical site infections (SSIs) are defined as either incisional or organ/organ space infections. Incisional SSIs are then divided into superficial, involving the skin and subcutaneous tissue, and deep, involving the muscle and fascia [1]. Typically an infection is considered an SSI if it occurs within 30 days of the operation. SSI rates vary by procedure with rates being highest with cardiac surgery (2.5 infections per 100 patient discharges) [2]. As estimated by the US National Nosocomial Infections Surveillance System, there are approximately 1.7 million heathcare-associated infections annually in US hospitals, of which approximately 22% are SSIs – second only to urinary tract infections [3]. This totals nearly 300 000 surgical site infections yearly (about two SSIs per 100 procedures) and an estimated 8205 excess attributable deaths [3]. Of all those that died with an SSI, 77% were found to have the infection causally related to their deaths [4].

It is recognized that a cost analysis for a medical intervention (e.g., an intervention to reduce SSI) is complex in its method of analysis and determination of outcome, and may not be accurately reported in the literature [5]. Nevertheless, there are many studies attempting to evaluate the cost of SSIs, and recent significant studies are summarized in Table 14.1. Reviews of the cost of SSIs have also been published by Yasunaga et al. [6] and Urban [7].

Risk factors

The incidence of SSIs varies depending on the surgeon, the hospital, procedure type, and individual patient risk factors. The fact that confounding factors such as procedure type, duration of procedure, comorbid conditions, and baseline severity of illness of patients can impact surgical infection occurrence necessitates the risk adjustment of SSI rates for fair comparison between surgeons and hospitals. Determination of risk factors is most useful when identified risk factors are modifiable. Therefore, factors such as specific hospital and procedure type may be interesting to note, but their identification as risk factors does not help surgeons, anesthesiologists, and infection control personnel prevent SSIs. In fact, duration of surgery, age, obesity, and underlying disease are some of the most commonly noted risk factors for development of SSI, yet they are fixed parameters from the perspective of the infection control practitioner. While it may seem that identifying an individual surgeon as a risk factor could be more disruptive than helpful, it has been shown that one of the most successful ways to reduce

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Table 14.1 Cost of surgical site infections by various estimates

Source reference	Subjects, no. (SSI/non-SSI)	Surgical procedure	Costs evaluated: type of SSI	Cost analysis	Cost
Olsen et al., 2008 [160]	888 (50/838)	Mastectomy, breast reconstruction	In-hospital, LOS Various	Crude cost	$4091
Jenney et al., 2001 [161]	216 (108/108)	CABG	In-hospital, LOS, antibiotic use Superficial, deep	Crude cost	$12 419 (AU)
Hollenbeak et al., 2000 [162]	201 (41/160)	CABG	In-hospital, total cost, LOS Deep	Crude cost	$18 938
Hall et al., 1997 [163]	6791 (176/6615)	CABG	In-hospital, total cost Unspecified	Crude cost	$23 200 (adjusted for variables)
Coskun et al., 2005 [164]	176 (88/88, 52 deep SSI, 36 superficial SSI)	CABG	In-hospital, LOS, antibiotic use, testing Superficial, deep	Crude cost	$6851 (deep) $3741 (superficial)
Whitehouse et al., 2002 [165]	62 (31/31): university 46 (23/23): community	Orthopedic	In hospital; variable, fixed and indirect costs Superficial, deep	Crude cost (median)	$38640 (SSI) $10671 (controls)
Perencevich et al., 2003 [166]	267 (89/178)	Various	Insurance provider database, all costs within 8 weeks post-discharge Unspecified	Crude cost	$5155 (SSI) $1773 (controls)
Kirkland et al., 1999 [167]	510 (255/255)	Various	In hospital, readmission within 30 days Superficial, deep	Crude cost	$8864 (SSI) $4391 (controls)
Herwaldt et al., 2006 [168]	3864 (438/3425, 438 nosocomial infections, 316 of which were SSIs)	Various: general surgical (2408), neurosurgical (732), cardiothoracic (724)	In hospital, 30 days postoperative Not described	Crude cost	$6364 (SSI only) $3343 (without infection)
Reilly et al., 2001 [169]	2202 (220/1982)	Various	In hospital, LOS, outpatient, home services Not described	Crude cost	£87 276
McGarry et al., 2004 [170]	286 (96/190, controls included 59 uninfected elderly and 131 younger patients with *Staphylococcus aureus* SSI)	Various	Hospital charges within 90 days postoperative Superficial, deep (post-cardiothoracic superficial SSIs excluded), due to *Staphylococcus aureus*	Crude cost	$41 117 (attributable cost compared with uninfected elderly) $2746 (attributable cost compared with younger patients with SSI)

(continued)

Source reference	Subjects, no. (SSI/non-SSI)	Surgical procedure	Costs evaluated: type of SSI	Cost analysis	Cost
Coello et al., 2005 [171]	67410 (2832/64578)	Various	Charge from prior study, adjusted for inflation, LOS Superficial, deep	Crude cost	£959-£6103 (depending on procedure) £814-£6161 (superficial) £1947-£6626 (deep)
Kasatpibal et al., 2005 [172]	280 (140/140)	Various	Hospital charge Not described	Crude cost	43658 baht
Dimick et al., 2004 [173]	1008 (75/933)	Various	In-hospital cost Superficial, deep, sepsis, wound dehiscence	Crude cost	$1398 (adjusted for variables)
Engermann et al., 2003 [174]	479 (186/193, 165 patients with MSSA SSI, 121 patients with MRSA SSI)	Various	In-hospital cost Superficial, deep	Crude cost (median)	$92363 (MRSA SSI) $52791 (MSSA SSI) $29455 (controls)

SSIs is proper surveillance of infection rates and feedback of rates to individual surgeons [8]. Throughout the rest of this section we will describe the evidence that supports specific risk factors for SSI with a particular focus on modifiable risk factors and randomized controlled clinical trials demonstrating improved outcomes with their modification.

Glucose control

Diabetes is known to increase the risk of developing a SSI. Unlike other comorbidities, such as obesity, there is a potential for lowering the risk of SSI through perioperative glucose control. One proposed mechanism includes improved neutrophil phagocytic function (but not antibody-dependent cell cytotoxicity), as demonstrated in a randomized trial of patients receiving either intensive or standard insulin treatment during surgery [9]. Furthermore, a recent review of the impact of hyperglycemia on the immune system suggests that despite limitations to the breadth of research, there is good evidence that the immune system is impaired with short-term hyperglycemia [10].

As a recent review of hyperglycemia and SSIs in cardiothoracic surgical cases points out, there is ample evidence to demonstrate an association between perioperative hyperglycemia and SSI risk [11]. In one study of cardiothoracic surgery patients, a postoperative glucose level greater than 200 mg/dL within 48 hours after surgery was shown to increase the odds of developing an SSI by 86% in known diabetic patients and by 114% in patients with no history of diabetes, and these results were largely unchanged with multivariable analysis [12]. Similarly, among 260 patients undergoing mastectomy (50 SSIs were observed; 37 superficial, 13 deep), the presence of any perioperative glucose value $\geqslant$150 mg/dL increased the risk of SSI three-fold, even after correction for the presence of diabetes [13].

Another group found that an elevated average blood glucose over the 48-hour postoperative period was the strongest predictor of deep sternal wound infection in diabetic patients undergoing open-heart procedures [14]. Additionally, they performed a quasi-experimental trial in which historical controls, who had perioperative blood glucose controlled with subcutaneous insulin injections, were compared to a later group who had continuous insulin infusions and found that continuous insulin infusion was associated with a two-third reduction in the risk of deep sternal wound infection [15]. Trials that use historical controls, however, are limited by the fact that additional changes may occur through time, which cannot be controlled for in the quasi-experimental design and could explain or partially explain the reduced infection rates.

Perioperative warming

Hypothermia is thought to increase a patient's risk of developing a SSI through thermoregulatory vasoconstriction and resultant reduced tissue oxygen levels,

and impairment immune function including T-cell-mediated antibody production and oxidative neutrophilic bacterial killing [16]. Unwarmed patients in surgery lose heat until their core temperature falls about 2°C, after which core temperature is stabilized by peripheral vasoconstriction and altered heat distribution [17,18].

Several limited studies have demonstrated an indeterminate relationship between perioperative warming and surgical site infections. A prospective cohort study of 290 patients undergoing laparoscopic cholecystectomies demonstrated that patients with mild perioperative hypothermia (156 with hypothermia, 105 without hypothermia) were more likely to have SSIs (18 in the hypothermic group, two in the normothermic group), but were also more likely to have a longer surgery. The role of age, diabetes mellitus, and prophylactic antibiotic use cannot be excluded as confounding difference, however [19]. A retrospective cohort study of 150 consecutive patients undergoing colectomy (101 normothermic patients and 49 patients with intraoperative temperature less than 95.5°F) found similar postoperative infection rates and postoperative length of stay between the two groups [20]. A relatively small case–control study among patients who underwent cesarean section with 18 cases who developed SSI compared to 18 controls found intraoperative temperature to not be a significant risk factor for the development of SSI [21]. In a small randomized controlled trial of 173 patients undergoing intracranial surgery in Japan, four of 122 patients (3.3%) randomized to intentional mild hypothermia (goal temperature 34.5°C) developed SSI, compared with none of the 51 patients randomized to normothermia [22].

Two randomized controlled trials, however, provide a clearer picture of SSI rates with control of perioperative temperature. In a randomized controlled trial in patients undergoing colorectal surgery, Kurz et al. demonstrated an approximately three-fold reduction in SSI rates in patients actively warmed approximately 2°C to the desired temperature of 36.6°C by intravenous fluid warming and forced-air warming in the intraoperative period [23]. The same study also found that patients who were in the hypothermic arm of the study had 20% longer hospital stay. In a randomized controlled trial of patients undergoing breast, varicose vein, or hernia surgery, Melling et al. found that warming patients before surgery reduced postoperative SSIs. Patients were randomized to one of the following: systemic warming (whole-body warming by blanket and forced air in the 30-minute preoperative period), localized warming (30 minutes of preoperative warming localized to the planned wound area), and nonwarming standard care [24]. The study found that both systemic warming (absolute risk reduction 7.9%, 95% CI 1.0–14.8) and local warming (ARR 10.1%, 95% CI 3.6–16.6) were associated with reduced SSIs compared to standard nonwarmed treatment. The study was not powered to find a difference between the systemic and local warming groups.

A broad recommendation across all types of surgery cannot be given since patients who undergo certain procedures actually benefit from hypothermia. Mild hypothermia has a documented cerebroprotective effect in neurosurgery patients [25], which would likely outweigh their very low risk of SSI [26]. In addition, core temperatures are lowered in cardiac surgery to protect the myocardium and central nervous system [18].

Supplemental oxygen

Neutrophilic bactericidal activity is mediated by superoxide radical-dependent oxidative killing, which is linked to the partial pressure of oxygen in the tissue [27]. A cohort study of patients at high risk for SSI found that the oxygen tension of the subcutaneous tissue measured perioperatively was a very strong predictor of subsequent development of SSI [28]. The infection rate was 43% (6 of 14 patients) in those with maximum oxygen tension between 40 and 50 mmHg and 0% (0 of 15 patients) in those with maximum oxygen tension above 90 mmHg. The wound hypoxia has been correlated with reduced leukocyte killing from depressed oxygen consumption and superoxide formation [29].

Greif et al. performed a randomized controlled trial in patients undergoing colorectal surgery compared patients who received 30% inspired oxygen to those receiving 80% inspired oxygen [27]. The oxygen was given intraoperatively and in the 2 hours after surgery. Even though arterial oxygen saturation was normal in both groups, the subcutaneous partial pressure of oxygen was significantly higher in those who received 80% inspired oxygen. Importantly the infection rate was only 5.2% in the 80% inspired

oxygen group compared to an infection rate of 11.2% in the 30% inspired oxygen group (ARR 6.0%, 95% CI 7.3–15.1%). The duration of hospitalization was the same in both groups. The study was ended early because of the significant benefit from supplemental perioperative oxygen. A subgroup analysis found that higher oxygen was not associated with any additional risk for radiologically confirmed pulmonary atelectasis [27].

Subsequently, a double-blind, randomized controlled trial among 165 patients undergoing major intraabdominal surgery compared SSIs within 14 days of surgery among 80 patients receiving 80% inspired oxygen (85 initially randomized) and 80 patients receiving 35% inspired oxygen (80 initially randomized) intraoperatively and 2 hours postoperatively [30]. Perhaps significantly, rates of obesity were higher in the 80% inspired oxygen group and rates of COPD were higher in the 35% inspired oxygen group, rates of blood loss and fluid resuscitation were higher and operation length were longer in the 80% inspired oxygen group, and the 80% inspired oxygen group were more likely to require postoperative intubation. Twenty patients in the 80% inspired oxygen group (25%) and nine patients in the 35% inspired oxygen group (11.3%) had SSIs ($P = 0.02$). Hospitalization duration and reoperation rates were higher in the 80% inspired oxygen group, though not statistically significant. Infection depth/location was not significantly different between the two groups. Significant limitations to this study include small sample size, analysis of infection rates by retrospective chart review, inadequate assessment of tissue perfusion and possibly oxygenation, and the above-mentioned differences in study groups [30].

Prompted by the discrepancy between these two trials, a randomized controlled trial similar in methodology to Greif et al. [27] also compared rates of SSI in 291 patients undergoing elective colorectal resection who received either 30% or 80% inspired oxygen intraoperatively and 6 hours postoperatively [31]. Other than measurements of Fi_{O_2} and Pa_{O_2}, the 143 patients in the 30% inspired oxygen and the 148 patients in the 80% inspired oxygen groups were similar. Perioperative use of 80% inspired oxygen was associated with a significant protective effect of postoperative SSI; among patients receiving 30% inspired oxygen, 35 (24.4%) had an SSI within a 15-day postoperative period, while 22 (14.9%) of those in the 80% inspired oxygen group had an SSI (RR 0.61, 95% CI 0.38–0.98). In multivariate analysis, only 30% inspired oxygen and coexisting respiratory disease significantly increased risk of SSI [31].

One potential risk of high oxygen concentrations during the perioperative period is the theoretical risk of atelectasis and subsequent pneumonia [30], although two studies addressing the issue of oxygen concentration, atelectasis, and lung function suggest that any difference may be negligible [32,33]. The studies by Grief and Belda provide methodologically sound evidence of postoperative benefit from perioperative supplemental oxygen. While oxygen supplementation is increasingly recommended for its apparent benefits and minimal risk [34], the best data to date is in the limited operative subset of colorectal surgeries, although these are at higher risk of infection than many other types of surgery [8].

Hair removal

Hair removal as part of the preparation of the surgical site has long been a practice of surgeons to improve exposure to the incision site and subsequent wound, facilitate wound closure and dressing, and has been thought to prevent SSIs. Three methods of hair removal are commonly practiced: shaving, clipping, and depilatory creams. It is now suspected that shaving changes the normal flora, removes the hairs' natural protective effect, and causes minor trauma which may allow for an entry site for bacteria or produce exudates that support bacterial growth; all of these factors when combined may increase the risk of infection [35].

The most comprehensive and recent review of the evidence for hair removal in reducing SSI rates is the Cochrane review on the topic published in 2008 [36]. After evaluating 11 randomized controlled trials, the authors concluded that hair removal prior to surgery did not affect SSI rates, although removing hair using a razor increased rates of SSIs compared with clipping or depilatory cream [36]. Two randomized controlled trials involving 358 adults undergoing abdominal surgery compared preoperative hair removal with no hair removal, each finding an absence of statistical difference between SSI rates. Pooled, 9.6% (17/177) of people who underwent shaving prior to surgery developed an SSI compared with 6.1% (11/181) of those

with intact hair (RR 1.59, 95% CI 0.77–3.27) [37,38]. Court Brown also investigated depilatory cream compared with no hair removal, and found SSI rates of 7.9% (10/126) and 7.8% (11/141) among patients receiving depilatory cream and no hair removal, respectively (RR 1.02, 95% CI 0.45–2.31) [37]. In three trials investigating shaving versus clipping [39–41], statistically higher rates of SSI were observed in the shaving group (2.8% [46/1627] vs 1.4% [21/1566], RR 2.02, 95% CI 1.21–3.36), although all studies had methodological limitations [36]. Seven trials among 1213 patients receiving varied types of surgeries compared hair removal with depilatory cream versus razor use [37,42–47]. Again, methodological variations and limitations are significant, however, pooled data demonstrates 7% (38/543) of patients receiving depilatory cream versus 10% (65/670) of patients who were shaved had postoperative courses complicated by SSI (RR 1.54, 95% CI 1.05–2.24) [36].

It appears that hair removal should be limited to situations where it will impede the operation and if necessary hair should be removed with clippers or depilatory cream and not a razor. Issues without definitive data include optimal timing of hair removal in proximity to surgery and optimal location to perform hair removal (i.e., ward, preoperative suite, or operating room) [36].

Smoking cessation

Rates of tobacco use in the United States remain above 20% of adults despite a slowed but continued decrease in rates in the last 50 years [48]. The causal association of tobacco use (smoking) and postoperative complications – including pulmonary and wound healing – is well-studied [49]. Smoking likely affects postoperative risk of SSI in mechanisms similar to hypoxemia, including inhibiting immune response [50], promoting peripheral vasoconstriction, disruption of endothelial function, and superoxide radical ion production [51].

Several cohort studies have demonstrated a positive association between smoking and SSI, including a four-fold increased risk of SSI among 1505 Veterans Administration patients undergoing ventral hernia repair [52], a 1.8-fold increased risk of superficial (though not deep) sternal wound infection among 4004 patients undergoing coronary artery bypass grafting [53], a 1.75-fold increased risk of SSI among 4855 patients undergoing open gastrointestinal surgery [54], and a 3- to 3.5-fold risk among patients undergoing breast cancer or reconstructive breast surgery [55,56]. Two smaller studies designed to analyze the risk of wound infections among smokers versus nonsmokers have also demonstrated significantly increased risk of SSI among smokers, in a populations of patients undergoing postbariatric abdominoplasty [57] and ambulatory surgery [58].

Although one small study of 60 patients undergoing elective colorectal surgery who were randomized to either short-term preoperative smoking cessation (2–3 week preoperative intervention) or continuation of habit demonstrated no significant difference in postoperative complications including wound infection [59], two randomized controlled trials have demonstrated a significant increase in postoperative wound infections in smokers. Sorensen et al. investigated an intervention of smoking cessation in reducing postoperative SSI risk among incisional wounds created by a punch biopsy [60]. In 48 healthy smokers, sutured incisional wounds were made to excise the previously made 5-mm full-thickness punch biopsy wounds at weeks 1, 4, 8, and 12 of the study; among 30 healthy never-smokers, identical wounds were made in six, and a one-time wound was made in the other 24 subjects. After the first week of the study, smokers were randomized to continuous smoking, smoking abstinence with transdermal nicotine patch, or smoking abstinence with placebo patch (each subgroup with eight men and eight women). At 1, 4, 8, and 12 weeks, continuous smokers had significantly more wound infections (total of 10 infections in 12 patients) than either abstinent smokers (one infection) or never-smokers (one infection).

Three Danish hospitals participated in a randomized controlled trial of 120 patients undergoing elective knee or hip arthroplasty. Sixty patients were randomly assigned 6–8 weeks prior to surgery to either a smoking cessation intervention with counseling and nicotine replacement or standard care. Among the 56 patients in the intervention group that completed the study, 36 stopped smoking, 14 decreased tobacco use, and six continued smoking; among the 52 patients in the control group completing the study, four stopped smoking and 48 continued smoking. Cardiovascular complications, repeat surgery, and wound-related complications were higher among the control group. Twelve patients (23%) had "positive culture" wound infections from the control

group, compared with only two patients (4%) from the intervention group ($P < 0.05$).

While the magnitude of effect and optimal time for cessation is not fully characterized, there is strong evidence that smoking contributes to SSI risk and that cessation prior to surgery decreases this risk. Due to SSI and other perioperative risk, as well as nonsurgical, noninfectious health risks, it is highly advisable to counsel patients to quit smoking prior to surgery.

Staphylococcus aureus elimination with mupirocin ointment and chlorhexidine scrub

Staphylococcus aureus is a frequent cause of SSIs, and data has suggested that nasal carriers of *S. aureus* may be at higher risk than noncarriers for SSIs [61]. Mupirocin ointment may be successful in eliminating nasal carriage of *S. aureus*. A large cohort study of cardiothoracic surgery patients using both concurrent and historical controls found between a 4.5% and 5.8% reduction in SSIs in patients treated with nasal mupirocin ointment started on the day prior and continued for 4 days after surgery [62]. An analysis using this same data found that perioperative mupirocin was cost-effective and in most settings would be cost-saving [63]. A second prospective cohort study among open-heart surgery patients (992 control patients and 854 patients receiving intranasal mupirocin the day prior surgery, the day of surgery, and 5 days postoperatively) found a 1.8% absolute risk reduction in SSIs (2.7% vs 0.9%) with mupirocin use, a significant difference that was sustained among diabetic patients, nondiabetic patients, and among deep and superficial surgical wounds [64]. In a study among orthopedic patients, perioperative mupirocin in addition to preoperative triclosan wash was found to decrease the rate of MRSA SSIs and nasal *S. aureus* carriage compared with the pre-intervention period. Among 420 cases pre-intervention, and 1758 case with intervention, the rate of MRSA SSIs decreased from 2.3% to 0.3–0.4%, without change in the rate of MSSA SSIs (1.6% to 1.4–2.0%) [65]. In the other orthopedic study to date, Gernaat-van der Sluis et al. compared 1260 historical controls with 1044 patients treated with muprocin perioperatively and found a statistically significant decrease in SSIs from 2.7% to 1.3%. Although the rate of *S. aureus* SSIs decreased from 1.1% to 0.7%, this difference was not statistically significant [66].

Four randomized clinical trials have been conducted to evaluate the role of mupirocin in reducing SSIs [67–70]. In a randomized, double-blind placebo-controlled trial published in 2002 by Perl et al. [69] among 3864 patients undergoing various surgeries, there was no significant difference between SSI rates among patients receiving mupirocin (152/1933, 7.9%) and those receiving placebo (164/1931, 8.5%) and there was no significant difference in *S. aureus* SSIs between both groups (2.3% vs 2.4%, respectively). For *S. aureus* carriers randomized to both groups, mupirocin resulted in a significant reduction in *S. aureus* carriage in the mupirocin group and not the placebo group. Nevertheless, despite a trend in decreased rates of nosocomial infections (total and *S. aureus* specific) and SSIs (total and *S. aureus* specific) between *S. aureus* carriers receiving mupirocin and placebo, this difference was only significant for nosocomial *S. aureus* infections. In a double-blind, randomized, placebo-controlled trial among 263 patients with nasal *S. aureus* carriage undergoing elective cardiac surgery in Toronto, patients randomized to mupirocin use demonstrated slightly higher – though not significant – rates of total, sternal, and leg infections (13.8% vs 8.6%, 5.4% vs 4.7%, and 8.5% vs 3.9%, respectively) [68]. There was a significantly higher rate of *S. aureus* nasal colonization carriage rates among patients receiving mupirocin versus those receiving placebo. Kalmeijer et al. [67] studied preoperative mupirocin versus placebo in 315 and 299 patients, respectively, undergoing orthopedic surgeries. SSIs were similar among patients receiving mupirocin (12/315, 3.8%) and placebo (14/299, 4.7%), including when analyzed by deep and superficial SSIs as well as *S. aureus* and endogenous *S. aureus* SSIs. Rates of nasal carriage eradication were significantly higher among mupirocin-treated patients than placebo-treated patients. Lastly, in a trial among 395 patients undergoing abdominal digestive surgery, 193 patients were randomized to receive mupirocin 3 days preoperatively and 202 patients were randomized to no treatment [70]. Although limited by the absence of reporting of *S. aureus* carriage and the predominance of gram-negative over gram-positive or mixed bacteria causing superficial and deep SSIs, there was no significant difference in the rate of SSIs among the two studied groups.

Taking the data in its entirety, there appears to be a suggestion that mupirocin may reduce SSI rates in cohort studies that is not borne out in clinical trials,

despite large studies and subgroup analysis. A recent review [71] and metanalysis [72] have a similar summary of the data. Though some authors argue that mupirocin use may be cost-effective [63,73], this analysis cannot be made prior to establishing its efficacy, and subsequently the risk of inducing mupirocin resistance [74]. Further studies may establish a clear benefit in populations of *S. aureus* carriers or specific surgeries.

Bathing with chlorhexidine or similar antimicrobial agent prior to surgery is an alternative and complementary strategy to minimize SSI, and has been demonstrated to reduce bacterial burden on the skin [75,76]. The most definitive summary of evidence to date is a Cochrane systematic review [77] investigating bathing or showering with skin antiseptics prior to surgery. The review identified six randomized controlled trials of over 10 000 patients, three of which (7691 patients) compared 4% chlorhexidine ("Hibiscrub" or "Hibiclens") with placebo scrub and three of which (1443 patients) compared bar soap with chlorhexidine and (in the case of two of these three trials) chlorhexidine with no washing. Although one of the trials comparing chlorhexidine with bar soap found a statistically significant difference in SSI [78], there are methodological concerns with the trial, and when combined with two other trials, found no significant difference [77]. Similarly, of the two trials comparing chlorhexidine scrub with no washing, there were methodological differences compared to each other and compared to present-day practice; one study found no significant difference in SSI rates [79] while the second study found a 2.9% absolute risk reduction with chlorhexidine use [80]. The remainder of the studies failed to show a statistically significant benefit in SSI rates after chlorhexidine use. Taken together, these studies do not produce conclusive evidence that preoperative chlorhexidine scrubs reduce SSI rates. Consideration for the use of preoperative chlorhexidine warrants further evaluation, balancing the generally low risk to the patient, but an as yet poorly defined risk of developing antimicrobial resistance, including possible promotion of *Acinetobacter* infections [81].

Perioperative antimicrobial prophylaxis

Not all surgeries require antibiotic prophylaxis. The initial step in deciding whether antimicrobial prophylaxis is indicated in a particular surgery is to determine which type of procedure will be performed.

Table 14.2 Surgical wound classification

Class I/Clean: Uninfected operative wound with no inflammation and the respiratory, alimentary, genital, or uninfected urinary tract is not entered. Cleans wounds are primarily closed and necessary drains are closed.
Class II/Clean-Contaminated: Operative wound with controlled entry into the respiratory, alimentary, genital, or urinary tract. Specifically, operations of the biliary tract, appendix, vagina, and oropharynx are included if no evidence of infection or break in sterile technique.
Class III/Contaminated: Open, fresh accidental wounds or ones with breaks in sterile technique, gastrointestinal spillage, or incisions in which nonpurulent inflammation is encountered are contaminated.
Class IV/Dirty-Infected: Presence of old traumatic wounds with devitalized tissue or ones with existing clinical infection or perforated viscera suggesting preexisting organisms prior to the operation.

Source: Mangram et al. [1].

Table 14.2 lists the surgical wound classification scheme, which is by definition a postoperative assessment of intraoperative wound contamination, since breaks in sterile technique and other intraoperative findings cannot be predicted preoperatively. This classification allows the surgeon to estimate preoperatively the wound class of a given operation. Antimicrobial prophylaxis is indicated for clean-contaminated wounds (class II), which is separate from the practice of bowel decontamination, and in clean wounds (class I) if the SSI might be a clinical catastrophe as would be the case in intravascular or joint prosthesis implantations [1]. Antimicrobial prophylaxis is not indicated in class III or IV operations since these would involve specific antimicrobial treatment and would not be prophylaxis.

There are several issues surrounding the use of prophylactic antibiotics during the perioperative period including the timing of antibiotic initiation and the duration of dosing in the postoperative period. Classen et al. in a large prospective cohort study determined the effect of prophylactic antibiotic timing on the rate of SSI in 2847 patients who had clean (class I) or clean-contaminated (class II) operations [82]. Patients who received antibiotics preoperatively, defined as zero to 2 hours prior to incision, had the lowest rate of SSI (0.6%). Higher rates of SSI were seen for perioperative administration, within 3 hours

after incision (1.4%),and in those that received antibiotics more than 2 hours before (3.8% SSI rate) and more than 3 hours after (3.3% SSI rate) the incision. A logistic-regression analysis confirmed that timing of antimicrobial prophylaxis within 2 hours prior to incision was associated with the lowest odds of developing an SSI. The authors estimated that 27 SSIs would have been prevented in the 1-year study period if optimal timing of antimicrobial prophylaxis within 2 hours prior to incision was completely adhered to [82]. More recently, a study investigating the timing of antibiotic prophylaxis in patients undergoing total hip arthroplasty confirmed the goal of administering antibiotics within an hour prior to incision [83]. It requires a great deal of institutional effort to insure that antimicrobial prophylaxis is appropriately timed. At one medical center a random sample retrospective chart review found that after shifting responsibility of antibiotic dosing to the anesthesiologist with assistance of the pharmacy personnel in selecting patients for prophylaxis, the percent of patients receiving antimicrobial prophylaxis within 1 hour prior to surgery rose from 38% to 88% [84].

Increasingly, it is demonstrated and recommended not only that antibiotics should be given within 60 minutes of the surgical incision, but also that the postoperative duration of antimicrobial prophylaxis should be less than 24 hours [85]. A metaanalysis of 28 randomized trials with 9478 patients compared single versus multiple dose antimicrobial prophylaxis in a broad range of surgical procedure types and found no difference between the two groups; random effects model (OR 1.04, 95% CI 0.86–1.25) [86]. Another metaanalysis of 25 randomized trials found that prophylactic antibiotics are effective in reducing SSIs in patients undergoing total hip and total knee replacement surgeries (RR 0.24, 95% CI (0.14–0.43), NNT = 30), but found no benefit for prophylaxis extended beyond 1 day postoperatively [87]. A recent cohort study of 2641 patients undergoing coronary artery bypass graft surgery determined that prolonged antibiotic prophylaxis (greater than 48 hours after surgery) was not significantly associated with less risk of SSI compared to shorter duration (<48 hours) antibiotic prophylaxis [88]. Interestingly, this study found that prolonged antibiotic prophylaxis beyond 48 hours after surgery was significantly associated with an increased risk of acquiring a clinical culture growing either cephalosporin-resistant enterobacteriaceae or vancomycin-resistant enterococci when compared to shorter-duration prophylaxis.

These findings support the current Centers for Disease Control and Prevention (CDC) guidelines for SSI prevention that suggest that a full therapeutic dose of a bactericidal agent be given early enough so that peak levels are present at the time of the incision (e.g., 1–2 g cefazolin no more than 30 minutes prior to incision) and that therapeutic levels be continued throughout the operation and for no more than a few hours after incisional closure [1]. Exceptions mentioned within these guidelines state that higher antibiotic doses should be used in obese patients and that initial doses of antibiotics in cesarean section should be given immediately after umbilical cord clamping.

Comprehensive interventions

Ultimately, no single method should be used to reduce SSI rates. A comprehensive infection control program that utilizes many of the above strategies mentioned will have the greatest benefit through additive independent mechanisms and a combined effect. A 4-year observational study of a cardiothoracic surgery service after the initiation of a comprehensive infection control program that included surveillance, feedback to the surgeons, chlorhexidine showers the night before and morning of surgery, hair clipping if necessary, antibiotic prophylaxis in the holding area 30–120 minutes prior to surgery, and elimination of iced cardioplegia solution along with other changes was found to significantly reduce the rate of SSIs (OR = 0.37; 95% CI 0.22–0.63). In addition there were trends toward reduced rates of deep chest infection and mortality [2]. As part of a 56-hospital National Surgical Infection Prevention Collaborative, 44 hospitals presented data on 35 543 surgical cases over a 12-month period during which a comprehensive plan to reduce SSIs was implemented [89]. Interventions included antibiotic timing within 1 hour of surgery, appropriate antibiotic selection, discontinuation of antibiotic within 24 hours of surgery, normothermia (intraoperative temperature >36°C), avoiding shaving surgical site, hyperoxia (FIO_2 >80%), and glucose control (≤200 mg/dL) and all interventions showed statistically significant improvement during the four 3-month periods evaluated. The overall SSI rate fell from 2.28% in the first quarter to

1.65% in the final quarter (statistically significant by Wilcoxon rank sum), though the month-to-month trend was not significant by Poisson regression analysis. Subsequently, the University of Virginia joined the initiative, and implemented the above interventions during colorectal surgeries except avoiding preoperative shaving (and also included the placement of Penrose drains in the subcutaneous space of patients with a body mass index $\geqslant$25). While comparing 132 patients during the study period with 175 historical controls, compliance with antibiotic guidelines showed statistically significant improvement and rates of normothermia and perioperative glucose values demonstrated nonsignificant improvement. SSI rates decreased from 26% to 16% ($P = 0.04$), as did mean length of stay [90]. Lastly, in a single-site study investigating effect of a protocol including appropriate antibiotic use (selection, administration pre- and postoperatively as above), normothermia ($>$36°C), and glucose control ($<$200 mg/dL), 379 patients undergoing intra-abdominal surgical procedures during the first four months of the protocol were compared with 390 patients followed during the last 4 months of the 11-month study period. There was statistically significant improvement in antibiotic selection and timeliness of administration, while cessation of antibiotic postoperatively remained above 90% and the incidence of hypothermia fell a nonsignificant 15% to 10%. The 30-day incidence of SSI decreased from 9.2% to 5.6% ($P = 0.07$) [91].

In conclusion, an optimal infection control program to limit SSIs in surgical patients should include surveillance for SSIs in the inpatient setting and if possible tracking of SSIs that manifest after hospital discharge, and the SSI rates should be fed back to individual surgeons. Evidence supports the use of preoperative smoking cessation, perioperative glucose monitoring and control, perioperative warming as feasible by procedure, supplemental oxygen intraoperatively and for several hours after surgery, hair removal if necessary by clipping, perioperative antimicrobial prophylaxis with dosing that allows peak levels to be achieved prior to incision (cefazolin about 30 minutes prior and vancomycin about 1 hour prior), and repeat dosing if necessary to maintain levels during the procedure, and discontinuation of antibiotic prophylaxis within a few hours after completion of surgery. Whether or not attempted eradication of potential pathogenic organisms with intranasal mupirocin or whole-body chlorhexidine wash decreases SSI risk is not fully established, and warrants further investigation.

Methicillin-resistant bacteria

Case presentation 2

A 45-year-old male with type 1 diabetes is admitted with a soft-tissue infection of the left foot. You are called by the patient's attending physician when wound cultures are positive for MRSA and *Pseudomonas aeruginosa*. The patient is being treated with vancomycin and piperacillin-tazobactam. The current plan for the patient is a course of antibiotics. No immediate surgery is planned although the patient may require arterial bypass surgery at some point. The attending physician asks you the following questions:

1. What should I do to prevent other patients from acquiring this patient's MRSA?
2. What is this patient's risk in terms of morbidity and mortality?
3. What is the role for decolonization in this patient?

As hospital epidemiologist, you decide to put the patient on contact precautions involving the use of gloves and gowns. You explain to the physician that the patient is at risk for an increased hospital length of stay. The patient is also at risk of increased mortality if he develops an MRSA bacteremia. You advise against decolonization in this patient and in this setting.

Carriage, colonization and infection: clinical presentation of MRSA

Staphylococci are gram-positive bacteria that are normal skin flora and MRSA, like MSSA, primarily colonizes and is most readily cultured from the nares but may also colonize adjacent structures, such as the perineum, wounds, burns, respiratory secretions (including among intubated patients), urine, and feces [92].

Carriers of *S. aureus* are classified as: (1) persistent carriers, (2) intermittent carriers, or (3) noncarriers [93,94]. Approximately 10–35% of healthy people are persistent carriers, 20–75% are intermittent carriers and 5–50% are noncarriers; persistent carriers are less

likely to have variation in *S. aureus* strains than intermittent carriers [93,94]. While cross-sectional studies demonstrate an approximately 35% carriage rate in the general hospitalized population, certain populations have increased rates of carriage, particularly those undergoing renal replacement therapy, those with insulin-dependent diabetes mellitus, those with HIV infection, and patients receiving repeat injections for allergies 93,94]. Among patients colonized with MRSA, long-term carriage rate seems to vary between 30% and 60% depending upon the patient population [95]. The prevalence of MRSA carriage in the general community has been harder to estimate, and is likely much lower than that among hospitalized populations. A metaanalysis of 10 studies performing surveillance cultures (among a total of 8350 persons) demonstrated a pooled prevalence of MRSA colonization of 1.3%. When studies were clustered by the risk-level study participants represent, the pooled prevalence ranged from 0.2% in the lowest risk populations to 5.4% in populations with MRSA-contacts or at-risk environments [96]. More recently, one study demonstrated a 1.0% prevalence of MRSA colonization in a random sample of 295 healthy subjects in four non-healthcare locations [97]. In a larger study of 9622 persons as part of the National Health and Nutrition Examination Survey (2001–02), *S. aureus* was identified in 32.4% of persons, and MRSA colonization among 0.8% of persons [98]. Lastly, it should be mentioned that, while the majority of studies investigate MSSA/MRSA colonization by surveying nasal carriage, there is evidence that solely sampling the nares may inadequately capture all carriers. In one study among 5041 hospitalized patients, healthcare workers, and blood donors, 37.1% had nasal carriage of *S. aureus* (with or without throat carriage), and 12.8% had throat colonization alone (representing 25.7% of all *S. aureus* carriers) [99]. Although few other recent data is available investigating this issue, it is suggestive that a strategy of culturing areas other than the nares (forehead, axilla, groin, rectum) might be more sensitive for detection of MRSA carriers [99–102].

Colonization with MRSA usually precedes infection with the organism and, as an example, *S. aureus* nasal carriage has been strongly associated with increased risk of developing a surgical site infection [61,93,94]. However, although it is thought that relatively few individuals colonized with MRSA spontaneously develop infections, this relationship has mainly been studied in a clinical population (not a general asymptomatic one) and many questions remain regarding the relationship between colonization and infection [103,104]. There is some data to suggest that colonization with MRSA on admission or during hospital admission increases the risk of MRSA infection [105,106].

MRSA causes a very broad range of infections, although the vast majority are skin and soft-tissue infections. Skin and soft-tissue infections may vary from cellulitis and SSIs to abscess, necrotizing fasciitis, and myositis. Infections may also be associated with indwelling catheters, including urinary catheters, intravenous catheters and central nervous system shunts, as well as surgical prostheses and implants. MRSA may also cause pulmonary infections including pneumonia with or without abscess or necrosis, empyema and ventilator-associated pneumonia, as well as endovascular infections and intraabdominal or renal abscesses.

Burden of illness of MRSA

The CDC's National Nosocomial Infections Surveillance (NNIS) system found that the percentage of inpatient MRSA isolates among *S. aureus* isolates rose from 2.4% in 1975 to 29% in 1991 [107]. The same reporting system found that, in 2003, there was an 11% increase in MRSA infections in ICU patients compared with the period from 1998 through 2002, with resistance rates of 59.5% among 4100 isolates. MRSA was found to be prevalent in all healthcare settings: median rates of MRSA isolates among *S. aureus* isolates among 157 intensive care units, 56 nonintensive care inpatient units, and 49 outpatient areas were 48.1%, 44.9%, and 24.6%, respectively [108]. The significance of high prevalence is not limited to the US. In a survey of bloodstream isolates from over 15 000 patients in the US, Canada, Latin America, Europe, and the western Pacific during the period 1997–99, MRSA prevalence ranged from 5.7% (Canada) to 46% (western Pacific region). Prevalence for specific countries ranged from less than 2% in the Netherlands and Switzerland to more than 70% in Japan and Hong Kong [109].

Death rates attributable to MRSA infections have been estimated to be 2.5 times higher than that

attributable to MSSA [110]. In one study, the mean cost attributable to MRSA infection was US$9275 [111]. MRSA infections have been shown to increase hospital length of stay by 4 days [111]. A metaanalysis was performed to assess the impact of methicillin resistance on mortality in *Staphylococcus aureus* bacteremia. Thirty-one cohort studies were included, 24 of which found no significant difference in mortality and seven of which found a significant difference. When results were pooled using a random-effects model, a significant increase in mortality due to MRSA bacteremia was evident (OR 1.93, 95% CI 1.54–2.42, $P < 0.001$). It should be noted that significant statistical hetereogeneity existed among the studies [112].

A recently published study demonstrated a notably high incidence rate of 31.8 invasive MRSA infections per 100 000 persons [113]. Among 8987 observed cases from the geographically and demographically varied Active Bacterial Core Surveillance/Emerging Infections Program Network in the US, collected from July 2004 through December 2005, 58.4% were community-onset healthcare-associated, 26.6% were hospital-onset heathcare-associated, and 13.7% were community-associated. Most significantly, the 988 deaths among 5287 hospitalized patients with MRSA infection reported in the study extrapolates to a nationwide death rate due to MRSA exceeding many other significant infectious causes.

The cost of MRSA-associated morbidity and mortality has likely not been fully estimated, although the difficulty and complexity of estimating the significance of antimicrobial resistance has been described [114]. It appears clear from available data that – whether due to confounding factors, strain differences, or treatment differences – MRSA takes a higher morbidity and mortality toll than MSSA, is a burden to the healthcare system in addition to (and not in replacement of) MSSA, and presents a patient and financial cost burden for many disease states beyond bacteremia [115].

Community-associated and healthcare-associated MRSA

Although MRSA had been identified in the community as early as the 1980s, these cases were strongly associated with populations such as intravenous drug abusers and residents of long-term care facilities who are frequently hospitalized. More substantial trends in community-associated MRSA (CA-MRSA) were reported by the mid- to late-1990s throughout the US [116] and elsewhere [117], and began to include case reports in the absence of predisposing risk factors [118,119]. CA-MRSA is defined by the characteristics in Table 14.3. CA-MRSA strains are currently classified by pulsed-field electrophoretic patterns (described as strains USA100 through USA1200), and currently USA300 is the major circulating strain.

Table 14.3 Clinical characteristics of community-associated MRSA infection

Develops within 48 hours of hospitalization
No history of MRSA colonization or infection
No indwelling medical device (including intravenous catheter) present at the time of isolation
No history of hospitalization, surgery, or hemodialysis within 1 year

Distinctions between HA-MRSA and CA-MRSA lie in the distinct spectrum of disease; resistance characteristics, and toxins expressed by each [116,119]. Two population-based studies in particular demonstrate these distinctions. In one prospective cohort study from 12 regionally varied laboratories in Minnesota in 2000 [116], 1100 MRSA isolates were identified as either CA-MRSA (131, 12%) or HA-MRSA (937, 85%) and compared for type of clinical infection, microbiologic characteristics, and exotoxin production; 3% could not be classified as either CA-MRSA or HA-MRSA. In this population, 25% (range from individual sites, 10–49%) of *S. aureus* isolates were methicillin-resistant. CA-MRSA patients were younger (median age 23 years vs 68 years), more likely to involve skin and soft-tissue infections (75% vs 37%), and were less likely to have respiratory or urinary tract infections than HA-MRSA patients. Among a representative sample, CA-MRSA isolates were generally susceptible to antimicrobials other than β-lactams and were more likely to be susceptible to multiple agents. Antibiotics which CA-MRSA was more likely to be susceptible to than HA-MRSA at a statistically significant rate were: ciprofloxacin (79% vs 16%), clindamycin (83% vs 21%), erythromycin (44% vs 9%), and gentamicin (94% vs 80%). Compared to HA-MRSA, CA-MRSA isolates were more likely to have distinct molecular features based

on pulsed-field gel electrophoresis (clonality) and had a higher prevalence of PVL genes (77% vs 4%). Although all isolates carried the *mecA* gene conferring methicillin resistance, SCC*mec* IV allele and *agr* 3 allele were more associated with CA-MRSA whereas SCC*mec* II and *agr* 2 were more commonly associated with HA-MRSA.

A study among 283 isolates in a California teaching hospital performed from December 2003 through May 2004 demonstrated similar results [119]: CA-MRSA most commonly caused skin and soft-tissue infections (86% of CA-MRSA isolates vs 42% of HA-MRSA isolates), CA-MRSA isolates were less likely than HA-MRSA isolates to cause urinary or respiratory infections; CA-MRSA isolates were more likely to be susceptible to ciprofloxacin and clindamycin (although neither CA-MRSA nor HA-MRSA were likely to be susceptible to erythromycin, and both were highly susceptible to gentamicin). This study is also notable for documenting high rates of USA300 clone (87% of CA-MRSA isolates, 33% of HA-MRSA isolates), a clone that is rapidly becoming ubiquitous. Very similar trends regarding spectrum of disease, microbiologic characteristics, and increasing prevalence rates have also been found in pediatric populations [120].

While not commonly evaluated, the distinction between HA-MRSA and CA-MRSA may prove significant in recognizing patterns of disease, transmission risk, and antibiotic selection. Further studies investigating these differences are warranted.

Risk factors for MRSA

The early literature on the topic identified risk factors for colonization or infection with MRSA including prior hospitalization, intravenous drug use, and comorbid conditions [121–130]. Numerous studies have demonstrated these categories as risk factors but unfortunately very few have concurred on common risk factors. Differences have arisen due to differences in study design/epidemiologic methodology [131,132].

A more recent trend developing through the 1990s to the present is the acquisition of MRSA (particularly CA-MRSA) in settings of close contacts and in populations with few to absent risk factors, although there is some data to suggest that the prevalence of MRSA among people who are truly without risk factors may be low [96,133,134]. Notable cases include transmission documented among a professional American football team [135], demonstrating the role of close contact and hygiene, and more recently, the emergence of a multidrug-resistant USA300 strain among men who have sex with men [136]. This latter case is of particular concern as CA-MRSA has traditionally had a more limited range of antibiotic resistance characteristics than HA-MRSA. The close contact among military recruits, incarcerated persons, and athletes has also proven to be a risk factor for transmission [135,137–141].

The relative causal component of risk factors for MRSA is still uncertain. In general, it is felt that MRSA incidence increases due to patient-to-patient transmission, with possible contributions from antibiotic use.

Preventive measures aimed at decreasing MRSA incidence

Hand disinfection and contact precautions

There is data that suggests that increased compliance with hand disinfection can reduce MRSA. A study by Pittet et al. demonstrated that institution of a whole hand hygiene program that included the institution of an alcohol-based hand disinfectant, compliance with hand disinfection increased from 48% to 66% and was associated with a decrease in the incidence of MRSA infections from 2.16 to 0.93 episodes per 10 000 patient-days. A limitation of this study is that it was a multifaceted intervention that included active surveillance, implementation of prevention guidelines, and the use of an alcohol-based hand disinfectant so it was difficult to determine the magnitude of benefit that was directly attributable to hand disinfection alone [142]. More recently, in a 2-year prospective study in the intensive care unit setting, investigators observed 17 994 minutes and 3678 hand hygiene opportunities in a crossover trial of alcohol-based hand gel [143]. Although rates of adherence to hand gel use improved markedly in both arms of the trial, there was no change in the rates of device-associated infection or infection with multidrug-resistant pathogens. This study throws into question the efficacy of alcohol-based hand gels as a *single* intervention in preventing transmission of multidrug-resistant organisms.

In the nosocomial setting, isolation or cohorting of patients identified as MRSA carriers or MRSA-infected and the use of contact precautions – disposable gown and gloves – is increasingly used to limit the spread of MRSA. Several studies have demonstrated the efficacy of isolation procedures and contact precautions in reducing rates of antibiotic-resistant organisms among hospitalized patients during outbreak investigations [144–149], but the mechanisms for this benefit are not well understood. One systematic review of studies evaluating isolation measures and the incidence of MRSA colonization and infection was published in 2004 [150]. The authors reviewed 46 studies, including 18 among isolation wards, 9 with nurse cohorting, and 19 involving other policies such as single bedded rooms, cohorting of patients, and barrier precautions. Shortcomings of the studies abound, including absent randomization (39 studies), significant differences in care for patients (e.g., differences in antibiotic use, lengths of stay; 31 and 29 studies, respectively), and lack of follow-up after discharge from hospital to reevaluate colonization or infection (all studies). Fourteen studies lack data warranting conclusions. In the six strongest studies, four demonstrated interventions (single room isolation, nurse cohorting, isolation ward) demonstrated control of major outbreaks, one demonstrated failure to control the epidemic, and one demonstrated initial success with eventual failure. Of the remaining studies, most demonstrated evidence of control, with some descriptions of failure. The CDC recommend contact precautions for healthcare workers caring for hospitalized patients with MRSA [151].

Active surveillance

Currently, there is ongoing debate about the benefit of active (or universal) surveillance as a strategy to reduce MRSA transmission and disease. The Dutch method of "search and destroy" – an aggressive and comprehensive surveillance program in addition to mandatory decolonization – has as evidence of efficacy the remarkably low rates of MRSA in that country [152,153].

While several studies have investigated a policy of universal screening in the ICU setting with mixed results, two recent studies investigate the value of universal screening in addition to a decolonization regimen for MRSA The first study, by Harbarth et al. [154], does not demonstrate a benefit to MRSA infection rates after implementation of universal screening and decolonization. In this study, surgical units at one major teaching hospital were divided into two groups, and using a control-intervention crossover design, implemented rapid MRSA screening of the nares, perineal region, and other sites ("when clinically indicated"). Both control and intervention arms underwent standard infection control measures and identified carriers underwent mupirocin and chlorhexidine decolonization. Among 10 910 control patients, 76 (0.7%) had identified MRSA infections, versus 93 of 10 844 (0.9%) during the intervention periods (incidence rate ration 1.2 per 1000 patient-days, 95% CI 0.9–1.7). There was no statistical difference in the rates of MRSA SSIs or in the incidence of nosocomial MRSA acquisition. Limitations to this study include a purely surgical setting and low rates of MRSA SSIs and infections.

In the second study, by Robicsek et al. [155], investigators followed a baseline year of routine surveillance with 1 year of nasal surveillance for all ICU admissions and subsequently 1 year of nasal surveillance for all hospital admissions; there were 39 521, 40 392, and 73 427 hospitalized patients during each period, respectively. Colonized patients were placed on contact isolation and were treated at the discretion of the treating physician with a 5-day decolonization regimen with mupirocin topical twice daily to the nares and a chlorhexidine wash every 2 days (during the third portion of the study only). The primary outcome – aggregate MRSA infection rate including bloodstream, respiratory, urinary tract, and surgical site infections within 48 hours of admission through 30 days post-discharge – demonstrated a 70% reduction in HA-MRSA in the intervention periods. However, several limitations include a quasi-experimental design, increasing adherence rates during the study periods, more rapid detection (PCR) during the universal period than the ICU period, and the uncontrolled addition of other interventions, including decolonization and isolation.

Decolonization

Many decolonization regimens have been used for MRSA, but typically employed regimens include the topical and systemic agents mupirocin, chlorhexidine, and rifampin. A good review on the topic has been published by Boyce et al. [156]. In one of the very few

prospective randomized controlled trials performed, Simor et al evaluated the efficacy of chlorhexidine, mupirocin, rifampin and doxycycline versus no treatment for the eradication of MRSA [157]. Among 146 patients from 8 hospitals identified as colonized (on admission or as part of an outbreak investigation) but not infected, 111 were randomized to study treatment and 35 were randomized to no treatment; at the primary outcome of 3-month follow-up, 87 patients and 25 patients could be evaluated in each group, respectively. Cultures were obtained from the nares, perineum, skin lesions, and catheter or medical device exit sites at study onset, weekly for 4 weeks, and monthly for an additional 7 months. Patients randomized to treatment received a 7-day regimen of 2% chlorhexidine gluconate washing daily, 2% mupirocin ointment to both nares three times daily, rifampin 300 mg twice daily and doxycycline 100 mg twice daily. At 3-month follow-up 74% (64 of 87) of those treated and 32% (8 of 25) of untreated patients remained culture-negative for MRSA (relative risk 1.55, 95%CI 1.17–2.04). At the end of the 7-day decolonization regimen, 92% of patients cleared MRSA from all sites; at eight months, 54% of 48 patients available for follow-up remained negative for MRSA. After multivariate logistic regression analysis, mupirocin-resistant MRSA at baseline was independently associated with recolonization with MRSA at 3 months, while functional status, presence of skin lesions, presence of a medical device and MRSA recovered from more than one body site were not associated with recolonization. Of significance, among 61 treated study participants with mupirocin-susceptible MRSA isolates at baseline, three (5%) had MRSA isolates with high-level mupirocin resistance in follow-up.

Prior to the Simor study, a Cochrane review of antimicrobial drugs for treating MRSA colonization summarized the six randomized controlled trials (384 non-healthcare worker participants) performed to date, and found "insufficient evidence to support use of topical or systemic antimicrobial therapy for eradicating MRSA" [158]. The six trials investigated: fusidic acid vs no therapy; mupirocin twice daily for 5 days vs placebo ointment; rifampin 600 mg orally twice daily vs minocycline 100 mg orally twice daily vs minocycline and rifampin (all for 5 days); mupirocin three times daily vs fusidic acid three times daily vs oral trimethoprim-sulfamethoxazole (TMP-SMX, DS) daily; ciprofloxacin 750 mg orally twice daily and rifampin 300 mg orally twice daily vs oral TMP-SMX (DS) twice daily (both for 14 days); novobiocin 500 mg orally twice daily and rifampin 300 mg orally twice daily vs. oral TMP-SMX (DS) twice daily and rifampin 300 mg orally twice daily (both regimens for 7 days). Outcomes of MRSA colonization (and in one case, infection) were reported at time points ranging from 12 to 180 days (typically 14). None of the trial endpoints demonstrated significant efficacy of any trial agents.

Guidelines

Recent Society for Healthcare Epidemiology of America (SHEA) [159] and Healthcare Infection Control Practicies Advisory Committee (HICPAC) [151] guidelines outline recommendations for the prevention of the spread and infection due to antibiotic-resistant organisms. Together, they each emphasize hand hygiene, environmental cleaning measures, and contact precautions for carriers, but diverge in their recommendations regarding active surveillance. SHEA recommendations advocate surveillance in high-risk populations while HICPAC recommends selective populations for surveillance.

In summary, active surveillance for MRSA in addition to strict isolation precautions and decolonization may help reduce transmission, however the process has neither been definitely proven nor disproven. Improving adherence to hand disinfection and investigating further the role of screening are worthwhile strategies.

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CHAPTER 15

Infections in neutropenic hosts

Stuart J. Rosser & Eric J. Bow

Case presentation

A 34-year-old male was admitted complaining of fever, generalized malaise, and increasing fatigue over the preceding 4 weeks. On examination, he was pale; his blood pressure was 122/78 mmHg; oral temperature 38.2°C, and pulse 110 per minute. His liver had a 14-cm span in the midclavicular line and the spleen tip was 10 cm below the left costal margin. Petechiae were present in the skin of the lower limbs. A complete blood count revealed a total leukocyte count of 35×10^9/L, an absolute neutrophil count (ANC) of 0.824×10^9/L, an absolute lymphocyte count (ALC) of 0.4×10^9/L, an absolute monocyte count (AMC) of 0.2×10^9/L, and a circulating blast count of 33×10^9/L. His serum uric acid was elevated at 590 μmol/L and his serum lactate dehydrogenase was 1890 IU/L. A chest roentgenogram was normal. A bone marrow examination revealed a hypercellular marrow specimen 90% infiltrated by blast cells, some of which contained Auer rods. Acute myeloid leukemia (AML) (French–American–British classification, M2) was diagnosed. A typical AML remission-induction regimen was administered, consisting of a 7-day continuous infusion of cytarabine plus an anthracycline, idarubicin, administered daily on days 1, 2, and 3. Beginning on day + 1 of cytotoxic therapy, ciprofloxacin 500 mg every 12 hours and oral acyclovir 800 mg every 12 hours were administered to prevent aerobic gram-negative bacterial infections and mucositis due to reactivation of herpes simplex virus respectively. Oral fluconazole 400 mg daily was administered to prevent superficial and invasive fungal infection due to *Candida albicans*. The blood cultures obtained at the time of hospital admission remained sterile and the fever resolved as the cytotoxic therapy was administered. The ANC fell to $<0.5 \times 10^9$/L on day + 3 of induction therapy and to $<0.1 \times 10^9$/L on day + 5.

Acute leukemia is a rapidly progressive disease. In the untreated patient, it results in early death owing to hemorrhage or infection – the consequences, respectively, of thrombocytopenia and neutropenia from marrow failure. Historically, infection has been the major contributor to mortality and has been designated as the primary cause of death in over one-third of acute leukemia cases. Notwithstanding advances in cytotoxic chemotherapy for the underlying malignancy and in the use of marrow-stimulating growth factors and antimicrobials to support individuals through their disease- and treatment-related marrow insufficiency, infection remains the major contributor to 66% of deaths in patients treated for acute myeloid leukemia (AML) [1]. The early recognition and appropriate treatment of infection remains a priority in the care of these profoundly immunocompromised individuals.

Case presentation (continued)

A detailed physical examination as well as diagnostic and microbiologic testing suggested no obvious infection, and the fever was subsequently felt to be disease-related.

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Neutrophils are the principal mediators of nonspecific (innate) cellular immunity. A deficiency in either the number or function of neutrophils can predispose an individual to infection. Diminished numbers of neutrophils, as opposed to qualitative defects in granulocyte function, are the more common cause of granulocytic immunodeficiency. While a total neutrophil count of $<1.0 \times 10^9$/L of blood defines neutropenia, the risk of bacterial and fungal sepsis rises exponentially below a level of 0.5×10^9/L. This profound degree of neutropenia occasionally results from an underlying inflammatory, infectious, or malignant condition, but is more often a consequence of the treatment of these diseases. In particular, the treatment of hematological and other malignancies with certain cytotoxic regimens will reliably induce profound and protracted neutropenia. Much of the data regarding the epidemiology, microbiology, diagnosis, and treatment of neutropenic sepsis is derived from studies of leukemia and bone marrow transplant patients. While there may be subtle differences in the characteristics of neutropenia-related sepsis arising from one disease state to the next, most of what we have learned from the hematology and oncology studies can be generalized to other conditions producing neutropenia of similar magnitude and duration.

The febrile neutropenic episode

Cytotoxic therapy for acute myeloid leukemia will predictably result in neutropenia, with absolute neutrophil counts of $<0.5 \times 10^9$/L for 10–14 days, or longer. While a patient may become febrile at any point during the course of treatment, the median time to first fever is typically 14 days from the first chemotherapy day [2], but may develop as early as day 9 (or about 3 days following the onset of neutropenia) [3]. The designation of a "febrile neutropenic episode" (FNE) applies when a neutropenic patient's oral temperature exceeds 38°C for at least 1 hour [4–6]. The fever itself arises from the production of proinflammatory cytokines (interleukin-1α, IL-1β, IL-4, IL-6, and tumor necrosis factor-α) [7], most often in response to either infection- or therapy-related cell membrane damage [8–12]. While fever is generally the first, and frequently the only sign of infection, not all febrile episodes will be the result of infection. The Infectious Diseases Society of America (IDSA) and the National Comprehensive Cancer Network (NCCN) define fever due to an infection as an episode associated with an oral temperature above 38.3°C (101°F) in the absence of noninfectious causes [4,6]. Some of the common noninfectious causes of fever in populations being treated for malignancies are outlined in Box 15.1. Febrile neutropenic episodes associated with infection may be further classified as microbiologically documented (either bacteremic or nonbacteremic) or clinically documented, where a site of infection is identified without a pathogen or where fever occurs without an alternate explanation. While a diligent search for infection may result in as few as 8% of febrile episodes being classified as "unexplained" [13], contemporary studies suggest that the actual proportion for which no infectious cause can be found may be as high as 35–60% [14–16].

Box 15.1 Fever in the neutropenic cancer patient: non-infectious causes

- Underlying malignancy
- Infusion of blood products
- Drugs: cytarabine, cyclophosphamide, hydroxyurea, polyenes (e.g., amphotericin B deoxycholate)
- Noninfectious inflammatory conditions: phlebitis, hematomas, thromboembolic disease

Measures to prevent infection in the neutropenic host

Protected environments

Non-antimicrobial measures aimed at preventing infections in patients with established or anticipated neutropenia have included: the placement of patients in a single room; the use of gowns, gloves, and masks by hospital personnel when entering patients' rooms; positive pressure ventilation in patients' rooms; and high efficiency particulate air (HEPA) filtration, with or without laminar (unidirectional) flow. A number of recommendations and guidelines regarding protected environments for high-risk patient populations have been published [17–23]. Most of the infections that occur during the pre-engraftment neutropenic period, however, represent reactivation of latent infection such as herpes simplex virus, or translocation of

bacteria or opportunistic yeasts colonizing mucosal surfaces damaged by cytotoxic therapies. The risk of airborne transmission of mold conidia has been shown to be reduced by HEPA-based protected environments [24,25]. A case-controlled, registry-based analysis among European patients undergoing allogeneic hematopoietic stem cell transplantation [26] and a retrospective analysis of the outcomes among transplant patients in Seattle [27] have suggested a survival benefit with the use of HEPA filtration. Despite these observations, prospective randomized studies have not been able to demonstrate an effect on the rates of invasive bacterial or fungal infections [26,28]. Although a systematic review of nonrandomized trials suggested a protective effect against invasive aspergillosis [29], no single study has been powered sufficiently to detect an effect of HEPA filtration on this relatively rare condition given event rates $<10\%$ in most neutropenic patient populations at risk [30,31]. It may be prudent to consider HEPA filtering with or without laminar flow for the protection of high-risk inpatients managed under circumstances where the invasive mold infection risk exceeds 6–8%, and where azole-based mold-active prophylaxis is not employed (see below). Such environments may include those in close proximity to hospital construction and maintenance projects [32]. As part of routine care, placement of patients in a single room and diligent hand washing on the part of healthcare workers and visitors are to be encouraged, while other protective measures should be reserved for high-risk patients (see Risk assessment, below).

Prophylactic antimicrobials

Antibacterial agents

The pathogens most commonly implicated in neutropenic sepsis are gram-positive and gram-negative bacteria derived from colonized skin and mucosal surfaces [33,34]. With this in mind, investigators have sought to prevent infections by reducing the burden of potential pathogens with antimicrobials. Initial efforts with oral, nonabsorbable agents had equivocal effects on infection-related outcomes in the neutropenic host [35–42] and had several economic and logistic drawbacks. Early studies using trimethoprim-sulfamethoxazole (TMP-SMX) showed reductions in bloodstream [43,44], microbiologically documented [43,45], and overall infections [45]. However, subsequent metaanalyses of studies comparing fluoroquinolone-based prophylaxis with TMP-SMX or with "no prophylaxis" showed that the risk of infection-related morbidity and mortality in TMP-SMX-treated populations was not significantly lower than for the groups receiving no prophylactic agent [46]. The latter finding may relate to the increasing prevalence over the past two decades of TMP-SMX resistance among aerobic gram-negative bacteria causing neutropenic sepsis [47,48].

Fluoroquinolones (principally ciprofloxacin and levofloxacin) have predominated as the agents of choice for antibacterial prophylaxis in the treatment of hematological malignancies since the mid-1990s. Multiple systematic reviews and metaanalyses have been published examining the role of systemic antibacterial prophylaxis in general, and of fluoroquinolone-based prophylaxis in particular, in neutropenic populations [46,49–55]. Protective treatment effects have been demonstrated for a number of clinically important outcomes including the frequency of febrile episodes, clinically and microbiologically documented infections, bloodstream infections, and gram-negative infections. Recent analyses have demonstrated a reduction not only for infection-related mortality, but for all-cause mortality, on the order of 33% [51,53]. Based on a pooled estimate of 6% all-cause mortality in groups treated without prophylaxis, the authors of these reviews estimate that prophylactic fluoroquinolone administration to 50 individuals would be required to prevent one death among patients with chemotherapy-induced neutropenia. Importantly, these studies have not identified an increased risk of infections with antibiotic-resistant organisms such as *Clostridium difficile*-associated diarrheal (CDAD) illness [52], notwithstanding evidence linking CDAD to fluoroquinolone use [56].

The benefits of fluoroquinolone prophylaxis are not restricted to those groups at highest risk for prolonged and severe neutropenia, such as the leukemic and stem cell transplantation populations mentioned above. A recent study from the United Kingdom evaluated levofloxacin-based prophylaxis in solid tumor and lymphoma outpatients at lower risk for neutropenic fevers [57]. The results demonstrated a significant reduction in febrile episodes attributable to infection and in hospitalizations for suspected infection by 29%

and 27%, respectively [57]. The majority of febrile episodes occurred during the first cycle of chemotherapy [58], as has been observed by others [59]. The risk for hospitalization for suspected infection was greatest for patients receiving chemotherapy for testicular cancers and small cell lung cancer, and among those with a poor baseline performance status [58]. The authors concluded that patients at risk should receive prophylaxis during cycle 1 of chemotherapy, but not during subsequent cycles unless a previous episode of febrile neutropenia had occurred. The reported all-cause mortality among low-risk recipients of fluoroquinolone *prophylaxis* compared to placebo has been 1.4% and 2.7%, respectively [53]. The all-cause mortality among low-risk patients receiving oral fluoroquinolones as part of empirical antibacterial *therapy* for neutropenic fever has been 1.7% and 2.5%, respectively [60]. The survival benefit appears to be in the use of fluoroquinolone therapy per se, rather than in the timing of that use, and there would seem to be no advantage to applying fluoroquinolone-based prophylaxis strategies among the low-risk patients with solid tumors and lymphoma, as compared to reserving those drugs for the ambulatory treatment of febrile neutropenic episodes in this population.

Based on the available evidence, the Infectious Diseases Working Party of the European Blood and Marrow Transplant Group, the European Leukemia Net, the Infectious Diseases Group of the European Organisation for Research and Treatment of Cancer, and the International Immunocompromised Host Society have endorsed the use of fluoroquinolone-based antibacterial prophylaxis in neutropenic patients undergoing induction therapy for acute leukemia or myeloablative hematopoietic stem cell transplantation [61]. The strongest endorsements were for ciprofloxacin (AI) and levofloxacin (AI). Further, the recommendations called for prophylaxis to begin with cytotoxic therapy and end with myeloid reconstitution or onset of a febrile neutropenic episode (AII). The National Comprehensive Cancer Network (NCCN) recently published recommendations for antibacterial prophylaxis based upon risk assessment [6]. The NCCN panel has not recommended prophylaxis for low-risk patients, defined as those for whom the expectation of the duration of cytotoxic therapy-induced neutropenia (ANC $<0.5 \times 10^9$/L) is less than 7 days. In contrast, prophylaxis might be considered for intermediate-risk patients: that is, those undergoing autologous hematopoietic stem cell transplantation, those receiving purine analog therapy, and those being treated with intensive therapy for lymphoreticular malignancies where the expected duration of neutropenia is 7–10 days. The panel continues to recommend prophylaxis for high-risk patients undergoing allogeneic stem cell transplantation, and those receiving intensive cytotoxic therapy for acute leukemia or myelodysplastic syndromes. In contrast, the German guidelines have endorsed prophylaxis for those undergoing allogeneic hematopoietic stem cell transplant [62], underscoring a lack of consensus based on the available evidence. Overall, the weight of opinion favors applying fluoroquinolone-based prophylaxis predominantly to those patients classified to be at high risk for neutropenic fevers.

The general enthusiasm for fluoroquinolone prophylaxis has been tempered by concern over colonization with, and subsequent infection by, fluoroquinolone-resistant gram-negative rods and gram-positive organisms against which the most frequently used fluoroquinolones have limited activity. Increases in the proportion of *E. coli* isolates resistant to fluoroquinolones within hematology-oncology populations have been widely recognized [63–65], notwithstanding a general decline in gram-negative bacteremic episodes among febrile neutropenics [66]. Analyses of the relevant trials [67] showed no significant increase in either colonization or infection with quinolone-resistant organisms when fluoroquinolone prophylaxis was compared to placebo ($RR_{Infection}$ 1.04; 95% CI 0.73–1.5); they showed a *reduced* risk of colonization or infection with resistant organisms when fluoroquinolones and TMP-SMX were compared ($RR_{Infection}$ 0.45; 95% CI 0.27–0.74, favoring quinolone prophylaxis) [52]. A similar reduced risk of bacteremic and other infections with gram-positive organisms has been noted (RR 0.44; 95% CI 0.38–0.51, for bacteremia), with no significant difference between fluoroquinolone and TMP-SMX-based regimens with regard to infection by gram-positive organisms. In consecutive two-period design studies at a single European centre [63,68], the suspension of routine fluoroquinolone prophylaxis for patients with chemotherapy-induced neutropenia resulted in an excess of bacteremic episodes involving fluoroquinolone-susceptible gram-negative organisms, and (in one study

period) an excess mortality [68], prompting early discontinuation of the study protocol. These studies attest to the efficacy of fluoroquinolone prophylaxis, even in settings where there is a moderate degree of preexisting fluoroquinolone resistance. While the available evidence supports the continued use of fluoroquinolones as antibacterial prophylaxis in the context of chemotherapy-related neutropenia, the generalizability of these findings to populations other than those with hematologic malignancies (studies of which comprised the bulk of the recent systematic review) is limited. Fluoroquinolone prophylaxis should continue to be reserved for those high-risk individuals whose duration of neutropenia is anticipated to be >10 days; whose neutropenia is expected to be profound (ANC $<0.1 \times 10^9$/L); and who are receiving treatment at institutions where the prevalence of quinolone resistance among facultatively anaerobic gram-negative bacilli is less than 15–20% [14]. In practice, the majority of these patients will be undergoing treatment for acute leukemia, myelodysplastic syndromes, or undergoing hematopoietic stem cell transplant.

Antifungal agents

Myeloablative conditioning regimens for hematopoietic stem cell transplantation and intensive cytotoxic therapies for acute leukemia predictably produce severe neutropenia (ANC $< 0.5 \times 10^9$/L) with durations of greater than 10 to 14 days [2,69]. Studies of antifungal chemoprophylaxis have traditionally focused on high-risk patients with acute leukemia (see discussion of Risk assessment, below), principally with regard to preventing infections due to yeasts. However, the incidence of invasive mold infection, predominantly due to *Aspergillus* spp. (in 90% of cases), has been increasing [70,71], making the prevention of these infections a higher priority. Filamentous fungi such as *Aspergillus* spp. are generally acquired through inhalation of conidia, which subsequently germinate to produce tissue-invasive disease. As such, they have been considered targets for environmental control measures (see discussion of Protected Environments, above) or mold-active antifungal chemoprophylaxis. Yeasts, on the other hand, colonize the mucosal surfaces of chemotherapy-treated patients, and are more prone to translocate across damaged epithelial surfaces, with subsequent invasive infections in the neutropenic host. These characteristics make yeasts an appealing target for orally administered prophylactic antifungal strategies.

A number of systematic reviews and metaanalyses of randomized-controlled trials on anti-fungal chemoprophylaxis have been published [72–76]. These analyses demonstrate that, in principle, antifungal chemoprophylaxis may improve important outcomes with respect to: invasive fungal infections (particularly where the baseline event rate for invasive candidiasis is >15% [74]); superficial fungal infections; attributable mortality due to fungal infection [73,75,77]; and even all-cause mortality, by almost 50% [77]. A reduction in all-cause mortality has only been demonstrated among the highest-risk patients, such as those with durations of severe neutropenia of >15 days [75] and those undergoing acute leukemia therapy or hematopoietic stem cell transplantation [77]. With regard to specific agents, systematic analysis has not demonstrated an advantage for itraconazole over that of fluconazole for invasive fungal infection overall [76], despite the anti-mold activity of the former agent. The formulation of itraconazole is an important confounding variable: the oral solution has better bioavailability than the capsules [73]. Moreover, daily dosing of >200 mg for fluconazole [75] or itraconazole solution [73] is required for maximum benefit.

Infections with filamentous fungi such as *Aspergillus* species, many of which will have their origin in a chemotherapy-induced neutropenic episode, are a major issue in the care of hematopoietic stem cell transplant recipients. Incidence rates for invasive aspergillosis among allogeneic stem cell recipients in the literature range from 2.9% to 16% (median 8.1%) [71], with attributable mortalities ranging from 36% to 87% (median 57.5%) [71]. Newer mold-active azole antifungals with significant activity against *Aspergillus* species have been evaluated in the context of chemotherapy-induced neutropenia, among them voriconazole and posaconazole. The data on voriconazole as a *prophylactic* agent in high-risk patients are sparse [78,79], and its utility in this setting has not been defined. Posaconazole has been compared to fluconazole and itraconazole in a prospective randomized clinical trial of prophylaxis for invasive fungal infections in patients undergoing remission-induction chemotherapy for acute myelogenous leukemia [30]: using standard definitions for *proven*, *probable*, and *possible* invasive fungal infection [80], its performance

was superior to the two comparators with regard to preventing *Aspergillus* infections. This benefit was attributed to an excess of *probable*, not *proven* infections in the fluconazole and itraconazole groups [30]. A second trial evaluated the prophylactic efficacy of posaconazole compared to fluconazole in allogeneic hematopoietic stem cell transplant recipients with acute or chronic graft-versus-host disease [31]. Similar protective benefits were observed among the posaconazole recipients, with a reduction of 68% in the risk for invasive aspergillosis. The number of patients requiring treatment to prevent one case of invasive aspergillosis was 19 [31]. The relative merits of prophylaxis with an expanded-spectrum azole such as posaconazole, versus a preemptive strategy of fluconazole prophylaxis and close serologic/radiographic monitoring have been reviewed elsewhere [30,81–83].

Recently published European guidelines advocate the use of fluconazole or posaconazole for the prevention of opportunistic yeast infections in patients undergoing hematopoietic stem cell transplantation (AI) [84]. Itraconazole (BI), the echinocandin micafungin (CI), and amphotericin B (CI) may be considered as alternatives. For acute leukemia patients undergoing induction or reinduction therapy posaconazole was favored (AI) over fluconazole or itraconazole (CI). The German guidelines are similar [85]. In contrast, the 2007 NCCN Guidelines endorse only fluconazole for the prevention of invasive candidiasis in acute lymphoblastic leukemia patients, arguing cytochrome P450 enzyme inhibition caused by agents such as itraconazole, voriconazole, and posaconazole may enhance the toxicity of the vinca alkaloids [6]. The NCCN panel recommended posaconazole or voriconazole prophylaxis for AML and MDS patients receiving intensive induction therapy, to be administered through myeloid reconstitution. Fluconazole or micafungin was recommended for autologous HSCT patients with mucositis. Antifungal prophylaxis with any of fluconazole, itraconazole, micafungin, voriconazole, or posaconazole should be considered for allogeneic HSCT recipients, and administered until at least day 75 after transplantation [6].

Adjuvant therapies

The association of infection-related morbidity with treatment-emergent neutropenia in oncology populations has spurred interest in the use of colony stimulating factors (CSFs) to decrease the incidence of febrile neutropenic episodes and their infectious complications. Six systematic reviews with metaanalyses evaluating the roles of CSFs have been published [86–91]. Primary prophylaxis – that is, the administration of colony stimulating factors following the administration of the cytotoxic therapy with each cycle, prior to a neutropenic event – has been shown to reduce the risk of febrile neutropenic episodes and infection-related mortality in general oncology populations [90], with a recent metaanalysis implying a substantial benefit with respect to early all-cause mortality (RR 0.599, 95% CI 0.433–0.830, favors CSFs) [92]. Despite these positive observations, another review of CSFs in malignant lymphoma patients failed to demonstrate a treatment effect for infection-related mortality (RR 1.37, 95%CI 0.66–2.82) [91], suggesting that efficacy differences may exist within subpopulations of cancer patients. Hematological malignancies by their very nature are not amenable to primary prophylaxis with CSFs, and aggressive secondary prophylaxis has generally been avoided in this context, in part because of lack of proven benefit, and in part because one retrospective study found that allogeneic hematopoietic stem cell recipients who received GCSF within the first 14 days after transplantation had both higher rates of acute and chronic graft-versus-host disease, and greater transplant-related mortality [69]. Two subsequent systematic reviews evaluating the use of granulocyte colony stimulating factor (GCSF) and granulocyte-monocyte colony stimulating factor (GMCSF) in hematopoietic stem cell transplant [87] and mixed hematology-oncology populations [93] have shown no increased risk of GVHD in the former group [87], and have demonstrated reductions in hospital length of stay [87,93], time to neutrophil recovery [93], and number of febrile days [87] with the use of CSFs. Borderline effects on both documented infections and infection-related mortality were also noted (upper limit of 95% CI = 1.0 for both). Given an estimated cost of US$20 400 per episode of febrile neutropenia complicating the treatment of a hematologic malignancy [94], the minor clinical benefits described above could have a significant cost benefit. The American Society of Clinical Oncology [95] acknowledged this potential impact in the most recent iteration of its guidelines for the use of colony-stimulating

factors, recommending CSF administration in post-remission consolidation therapy for acute myeloid leukemia, and for established febrile neutropenic episodes with high-risk indicators (see Risk assessment, below).

Case presentation (continued)

By day + 9, the patient complained of pain with swallowing. On day + 12, he complained of chills, muscle aches, headache, and abdominal discomfort. His oral temperature was 39.2°C, respiratory rate 26 per minute, pulse 100 per minute, and blood pressure 122/72 mmHg lying down and 98/60 mmHg standing. The oropharynx was diffusely erythematous with ulcerations over the hard palate and right buccal margin. There was no lymphadenopathy. The chest examination revealed inspiratory râles over the right medial basal segment. The abdominal examination revealed normal bowel sounds, but focal tenderness over the right lower quadrant was noted with light palpation. The ANC and AMC were 0, the ALC 0.3×10^9/L, and the platelet count was 12×10^9/L. A chest roentgenogram was unremarkable. Blood cultures were obtained from each lumen of the central venous catheter and from a peripheral site. Intravenous fluids, and empirical antibacterial therapy with a third-generation cephalosporin, ceftazidime, were administered; 24 hours later the blood cultures from all catheter lumens were reported as growing gram-positive cocci in chains. The patient remained febrile. Further blood cultures were obtained and vancomycin was empirically added to the ceftazidime.

Assessment and management of the febrile neutropenic episode

Most neutropenic patients with infections present with fever, whether or not a definable clinical focus of infection can be identified. Accordingly, the most important component of the clinical assessment of these patients is having an index of suspicion. The time course for a neutropenic episode is referenced from the first day of the current cycle upon which the patient received cytotoxic therapy. Most neutropenic fevers occur after the first week [3] at a median of day +14, and coincide with the time of maximal cytotoxic therapy-induced intestinal mucosal damage [2,96].

When a patient with an absolute neutrophil count of $<0.5 \times 10^9$/L meets the temperature criteria for a febrile neutropenic episode, vigorous attempts to document a source and/or to isolate a potential pathogen must be made. This requires a focused physical examination, and a minimum laboratory evaluation consisting of a full blood count, creatinine, liver enzyme tests, a chest radiographic examination; cultures of urine and sputum if urinary or respiratory symptoms are present; and cultures of blood drawn from each of two sites including each lumen of any indwelling venous catheter, as well as blood from at least one peripheral site. The latter recommendation derives from a study of neutropenic cancer patients [97], in which a negative culture from either a central or peripheral site had a predictive value for the absence of "true bacteremia" of 98–99%. A positive culture at either site had a predictive value for the presence of "true bacteremia" that was substantially lower (63% for the central venous catheter, 73% for the peripheral site). Overall, single negative cultures from the central or peripheral sites are more helpful in ruling out a true bacteremia than single positive cultures are at ruling it in. The high negative predictive values were not sensitive to changes in overall prevalence of true bloodstream infection.

If infection is suspected, empirical therapy with broad-spectrum antimicrobial agents should be instituted. Consensus recommendations also advise that any neutropenic individual with a clinically suspected infection should receive treatment, even in the absence of fever [4]. The choice of empiric therapy will be influenced by the results of the physical examination and key laboratory tests, by whether or not the individual's circumstances suggest a low risk for serious infection (see below), and by an understanding of which endogenous microflora cause infections most often in this population.

Physical examination

The salient features of a focused history and physical examination, as they pertain to the evaluation of a febrile neutropenic patient, are summarized in Table 15.1. The classic signs of inflammation associated with pyogenic infection in an immunocompetent individual may be absent or diminished in the context of absolute neutropenia. A seminal descriptive analysis of presenting signs and symptoms for

Table 15.1 Physical examination of the febrile neutropenic patient

Region	Examine for
Head and neck	
– fundi	Retinal hemorrhages (bleeding diatheses) Retinal exudates (disseminated fungal infection)
– auditory canals/tympanic membranes	Erythema (otitis externa/media; viral upper respiratory infection) Vesicles (herpetic infection)
– anterior nasal mucosa	Ulcerations/vesicular lesions (fungal disease, herpetic infection)
– oropharynx	Mucositis (predisposition to bacteremias/fungemias) Ulcerative gingivo-stomatitis (anaerobic bacteria) Pseudomembranous pharyngitis (thrush, a risk for candidemia)
Chest	Râles (more consistent than cough/sputum in diagnosis of pneumonia) Edema, pain, erythema around central venous catheter tunnel and exit sites
Abdomen	Localized tenderness (right lower quadrant: typhlitis; right upper quadrant: hepatobiliary infection; perianal tissues [not a digital rectal examination]: cellulitis, abscess or fistula)
Skin	Tenderness, erythema, swelling around intravenous sites Ulcerative or necrotic lesions (*Pseudomonas aeruginosa*, *Staphylococcus aureus*) Diffuse pustular/erythematous lesions (metastatic seeding with *Candida* spp.) Vesicular lesions (herpes simplex/zoster) Hypersensitivity reactions

neutropenic versus non-neutropenic hosts [98] showed that, with regard to skin and soft-tissue infections, edema was reduced in neutropenic patients (73% of neutropenic vs 100% of non-neutropenic individuals, $P = 0{\cdot}02$), while fluctuance and exudation were for the most part absent (5% vs 50%; $P = 0.003$; and 5% vs 92%; $P < 0.001$, respectively) [98]. Where pneumonia was ultimately diagnosed, cough and sputum production were less frequent among neutropenic patients (67% vs 93%, $P = 0.002$; and 58% vs 85%, $P = 0.003$, respectively), but bacteremia was more common (55% vs 17%; $P < 0.001$) [98]. This effect of neutropenia on the presentation of bacterial sepsis must be taken into account in the evaluation of the patient. The basic vital signs including the temperature, heart rate, and respiratory rate, together with the neutropenic state can be used to estimate a SIRS (systemic inflammatory response syndrome) score which may correlate with the risk for bloodstream infection or progression to more severe sepsis syndromes [99,100].

Risk assessment

"Risk" in neutropenic patients may be defined differently, depending upon circumstances. The Infectious Diseases Working Party of the German Society of Hematology and Oncology defines risk in terms of the *likelihood of developing* a febrile neutropenic episode [5]. The European Organisation for Research and Treatment of Cancer defines risk in terms of *failing to respond* to initial treatment of a febrile neutropenic episode, and of *complications* arising from the neutropenic episode that necessitate or prolong hospitalization, all in the context of clinical trials of empirical antibacterial therapy.

An individual's estimated risk for developing serious complications related to infection during a febrile neutropenic episode will have a bearing on the type of empiric antimicrobial therapy that is recommended and the setting in which it is administered. The concept of infection risk in this population has been more extensively reviewed elsewhere [101–103]. Patients may be conveniently divided into low, intermediate, and high-risk groups.

Low-risk individuals are those for whom the duration of neutropenia is expected to be short (3–5 days), who are clinically stable and without significant comorbidities, and who are ambulatory. These individuals may be treated empirically with oral antibacterial agents during their febrile neutropenic episodes, where the following circumstances apply:

- the individual is judged to be compliant
- immediate access to medical care is available in the event of deterioration
- a caretaker is present to monitor the patient.

Intermediate-risk patients are those with solid tumors or lymphoproliferative malignancies who are undergoing stem cell transplantation and who may therefore be expected to have a more prolonged period of neutropenia (8–13 days). By definition they should have minimal comorbidity and be clinically stable. They are treated initially with inpatient intravenous therapy and, if an early response is achieved, they may be "stepped down" to complete a course of further intravenous or oral therapy as an outpatient. High-risk patients are those receiving treatment for hematological malignancies (cytotoxic chemotherapy and/or stem cell allografting) for whom the duration of severe neutropenia will be protracted (>14 days), who may have significant comorbidities, or who are unstable (hemodynamically). These patients are much more likely to develop medical complications or to die [104], and should be treated as inpatients with intravenous antibiotics until their febrile neutropenic episode resolves.

The dichotomization of febrile neutropenic patients into only low-risk and high-risk categories with regard to recommendations for empiric antimicrobial therapy has also been advocated [4]. Here, the assessment of risk relies on a validated scoring system developed by a multinational collaborative group, in which treatment for a solid tumor, young age, outpatient status, and the absence of hypotension, symptoms, or significant comorbidity result in higher point scores: achieving a higher total point score (≥21) defines an individual as being at "low risk" for complications, and warrants the management outlined above for low-risk patients [105,106]. The positive predictive value of this point score (that is, the likelihood that an individual with a score of ≥21 will not experience a complication) is estimated to be 90–98% [103,106]. When used to inform decisions regarding the disposition of 383 first febrile neutropenic episodes at a single institution, the scoring system performed well, with only 4% of those patients discharged at less than 48 hours requiring readmission [107]. However, 38% of "low-risk" individuals in that study who could have been discharged but who remained in hospital had no objective medical reason for doing so, suggesting that the outpatient management of febrile neutropenic episodes was not universally endorsed [107].

Spectrum of bacterial infections in neutropenic cancer patients

In previous decades more than 75% of the systemic infections in patients dying with acute leukemia were due to enterobacteriaceae (*Escherichia coli*, *Klebsiella pneumoniae*), *Pseudomonas aeruginosa,* or *Staphylococcus aureus* [108,109]. More recently, gram-positive organisms have come to predominate as the etiologic agents of bacteremic infections. This shift may be related to several factors, including:

- the widespread use of central venous access catheters [110], which predictably results in a greater incidence of bacteremia with gram-positive skin colonizers such as the coagulase-negative staphylococci
- more intensive chemotherapeutic regimens, with greater toxicity to the gastrointestinal mucosa [111–113] and easier access to the bloodstream for viridans group streptococci and enterococci
- fluoroquinolone chemoprophylaxis, which suppresses the aerobic gram-negative bacilli colonizing the gut epithelium, but not the coexistent microaerophilic streptococci or coagulase-negative staphylococci.

It is therefore prudent to ensure adequate coverage for gram-positive pathogens in any empiric antibacterial regimen, particularly if the individual has received fluoroquinolone chemoprophylaxis. However, the risk of infection-related mortality is still highest for aerobic gram-negative bacteremic infections, particularly when *P. aeruginosa* is the causative agent [114], and recommended empiric antibacterial regimens include specific coverage for the latter organism.

Choice and duration of empirical antibacterial therapy

Table 15.2 lists a range of single-agent and combination antimicrobial regimens that have been used successfully in the management of fever from suspected infection in the neutropenic host. Low-risk patients

Table 15.2 Empirical antibacterial regimens for the management of febrile neutropenic episodes

Regimen type	Antimicrobial type	Examples
Monotherapy	Anti-pseudomonal penicillin+ β-lactamase inhibitor	Piperacillin/tazobactam Ticarcillin/clavulanate
	Carbapenem	Imipenem/cilastatin, meropenem
	Fluoroquinolone*	Ciprofloxacin, levofloxacin, moxifloxacin
	3rd or 4th generation cephalosporin	Ceftazidime, cefepime, ceftriaxone,** cefixime**
Combination therapy	Antipseudomonal β-lactam +	Piperacillin, carbapenem, or antipseudomonal cephalosporin
	Aminoglycoside or	Gentamicin, tobramycin, amikacin, netilmicin
	Fluoroquinolone	Ciprofloxacin, levofloxacin

* Outpatient therapy in low-risk patients not receiving fluoroquinolone-based antibacterial chemoprophylaxis.
** Outpatient therapy in low-risk patients.

for whom oral therapy is deemed appropriate may be treated with ciprofloxacin and amoxicillin-clavulanate, if the former drug has not been administered as part of a prophylactic regimen. Vancomycin may be added to an empiric regimen at the start of treatment if infection of an intravascular device is suspected (and coagulase-negative staphylococci are therefore implicated), or if the individual is known to be colonized with a β-lactam resistant gram-positive pathogen [115] such as methicillin-resistant *S. aureus*. Alternatively, it may be added to a regimen between days 3 and 5 of antimicrobial treatment, if the patient remains febrile, and if the chosen empirical regimen is judged to have suboptimal coverage for *S. aureus* and streptococci (e.g., ceftazidime monotherapy). However, given that 40% of patients with gram-positive bacteremias may respond to these regimens (i.e., ceftazidime alone) [116–118]; that vancomycin use has been associated with an increased risk of colonization and infection with glycopeptide-resistant enterococci [119–121]; and that the early/immediate addition of a glycopeptide provides no advantage in terms of mortality or time-to-resolution of the febrile episode [122], the routine use of vancomycin in empiric regimens is not recommended. A recent systematic review [123] suggests that β-lactam monotherapy options are equivalent to dual-therapy regimens in terms of both mortality and other less rigorous endpoints, with two possible exceptions: cefepime monotherapy has been associated with higher all-cause mortality in both the review (RR 1.44, 95% CI 1.06–1.94) [123] and a subsequent randomized controlled trial [15]; and the carbapenems (principally imipenem/cilastatin) have been associated with a greater risk of *C. difficile* toxin-mediated diarrhea (RR 1.94, 95% CI 1.24–3.04) [123]. Notwithstanding these distinctions, and acknowledging that individual patient factors (renal impairment, allergy) may also influence the choice of antibacterial agents, the selection of any particular regimen will depend more on institutional practice and local antimicrobial resistance patterns than on a proven survival benefit for any single drug or combination therapy.

Patients who are profoundly neutropenic, who remain febrile (without a documented source of infection) despite 5–7 days of empirical antibacterial therapy, and for whom neutrophil counts are not expected to recover in the short term are at high risk (approximately 20%) for invasive fungal infections [4,124]. Empirical antifungal therapy is felt to reduce the risk of invasive fungal infection in these patients by anywhere from 50% to 80%, and to reduce mortality from fungal infections by 23–45% [116–118]. Early studies of empiric amphotericin B therapy in febrile neutropenic cancer patients – where amphotericin B was added to background antibacterial therapy, at doses of 0.5–0.7 mg/kg/day – showed a trend towards reduced morbidity and mortality attributable to fungal infections, particularly in the highest-risk subgroups [125]. Overall, the available data justified a BII recommendation (B – should usually be offered;

II – based on clinical trials, with [at least] laboratory endpoints; United States Public Health Service/Infectious Diseases Society of America rating scheme) for the use of amphotericin B deoxycholate, or any antifungal agent in the neutropenic patient who remains febrile on broad-spectrum antibacterials for >3 days, if the neutrophil counts are not expected to recover in the ensuing 5–7 days. Other antifungal agents, such as the lipid-based formulations of amphotericin B [126–129], intravenous itraconazole [130], voriconazole [131], and the echinocandin caspofungin [132] appear to have equivalent efficacy to amphotericin B deoxycholate as empirical antifungal therapy in neutropenic hosts. Toxicity and pharmacoeconomic considerations may lead to the eventual replacement of conventional amphotericin B deoxycholate therapy with one or more of these newer options.

The decision to modify or discontinue empirical antibacterial or antifungal therapy will be influenced by several factors. If a specific microbe is isolated and implicated as the cause of the febrile episode, the spectrum of antimicrobial therapy can be narrowed to cover that organism (or group of organisms), and an appropriate course of therapy should then be undertaken for the organism and anatomic site involved. Other decisions regarding continued antimicrobial therapy will depend on the resolution of the febrile episode, and the recovery of the neutrophil count to $>0.5 \times 10^9$/L.

The median time to defervescence for low-risk patients is 2–3 days [133,134], while for high-risk patients it is 4–6 days [13,117,135,136]. Given these parameters, and in the absence of a positive culture, a documented source of infection, or clinical deterioration, changes to the empirical regimen are generally not warranted for the first 5 days of the febrile episode. Otherwise, expert opinion suggests the following guidelines [4]:

- Patients who defervesce within the first 5 days of empirical therapy should have their treatment continued for a total of at least 7 days; low-risk patients may step down to oral therapy; high-risk patients should continue on their intravenous medications.
- Patients who remain febrile, in the absence of an identifiable source of infection, should have their antimicrobial agents continued until 4 or 5 days after their neutrophil counts rise to $>0.5 \times 10^9$/L, or, if the counts do not recover, to a total of 2 weeks' treatment; the patient must be in stable condition prior to stopping the antimicrobials, and the need for further antimicrobials should be assessed on an ongoing basis, until the neutrophil count recovers.

Case presentation (continued)

The patient remained febrile over the first 5 days of antibacterial therapy. The gram-positive organism in the blood cultures was identified as a viridans group streptococcus (*S. mitis*). By day + 17 of induction therapy (day +5 of antibacterial therapy), the patient remained febrile with oral temperatures peaking daily between 38.5ºC and 39ºC and continued to complain of right lower quadrant pain, now associated with diarrhea and signs of peritoneal irritation. Stool cultures grew no pathogenic bacteria or yeasts, and a test for *Clostridium difficile* toxin A and B in the liquid stool was negative. Repeated blood cultures and chest roentgenogram were ultimately nondiagnostic. A computer tomographic examination of the abdomen identified cecal and ascending colonic wall thickening, with additional thickening of the ileal wall and the sigmoid colonic wall, consistent with neutropenic enterocolitis. The patient was treated with metronidazole intravenously. Over the course of the next 72 hours (until day + 20 of induction), the fever persisted; however, the patient's condition stabilized. The volume of diarrhea decreased and the abdominal pain, while still present, began to subside. The ANC and AMC were 0.001 and 0.2 $\times 10^9$/L, respectively. By day +22, the ANC, AMC, and platelet count were 0.186, 0.8, and 37 $\times 10^9$/L, respectively, consistent with marrow regeneration. The fever had abated, and the diarrhea resolved.

Selected infectious problems in the neutropenic host

Some infections in the neutropenic host may be anticipated. For example, in the clinical example above, a viridans streptococcal bacteremia in the context of mucositis with ciprofloxacin prophylaxis and empiric therapy with ceftazidime – neither of which affords reliable coverage for gram-positive organisms – is not unexpected. Certain other infectious syndromes are relatively common in the neutropenic host, and deserve specific attention.

Neutropenic enterocolitis

Neutropenic enterocolitis presents with a clinical triad of persistent fever, abdominal pain, and diarrhea. The spectrum of pathology ranges from mild mucosal inflammation to transmural necrosis. In a pooled analysis of case series and cohort studies evaluating individuals treated for acute leukemias, the incidence rate was estimated to be 5.6% (95% CI 4.6–6.9%) [137]. The likelihood of developing neutropenic enterocolits depends not only on the intensity of the chemotherapeutic regimen [138], but the type of chemotherapy, e.g., taxane-based therapy for solid tumors [139,140]. Onset of the first sign of neutropenic enterocolitis, diarrhea, occurs at a median of 9–10 days from the start of chemotherapy [141,142] and the syndrome is diagnosed at a median of 15 days from the start of chemotherapy [141]. The condition must be differentiated from other common causes of diarrhea in neutropenic cancer patients, including *Clostridium difficile* toxin-mediated diarrhea, and the direct effects of antimicrobial and cytotoxic agents. Abdominal computed tomography or ultrasound examination will typically show thickening of the bowel mucosa [143,144], with more frequent involvement of the cecum: a bowel wall thickness of >4 mm is considered suggestive, if not diagnostic [144]. The condition is associated with a high risk for translocation of, and subsequent bloodstream infection with, bacteria and yeasts.

Treatment is supportive, with fluids, blood products, analgesics, parenteral nutrition, and broad-spectrum antimicrobial therapy, including specific coverage for anaerobic bacteria. It is not uncommon for the fever associated with this condition to persist until resolution of the neutropenic episode, as in the case above: the addition of empirical amphotericin B therapy to this patient's antimicrobial regimen in the context of continued fever on broad-spectrum antibacterials was not considered necessary, given the diagnosis of neutropenic enterocolitis. Surgery is reserved for cases with perforation or refractory bleeding, and most patients can be managed medically [143].

Infections of intravascular devices

Central venous catheters are commonly implanted in patients undergoing protracted courses of chemotherapy, both for the administration of medications and for blood sampling. These catheters have up to a 20-fold increased risk of infection compared with peripheral devices [145]. Infection may occur at any point along the length of the device and, epidemiologically, these infections may be categorized [146] as:

- exit site infections, with <2 cm of inflammation at the site where the catheter leaves the skin
- tunnel infections, with >2 cm of inflammation, extending proximally from the exit site
- port pocket infections, where inflammation with or without fluctuance overlies the buried access bulb of a completely implanted system
- a catheter-related bloodstream infection, where blood cultures drawn from the device lumen(s) are positive.

Tunnel infections account for up to 50% of line-related infections; exit sites for 25%; febrile bacteremias (bloodstream infection) for 19%; and septic thrombophlebitis for 6% [147]. A bloodstream infection is generally attributed to an intravenous catheter if positive blood cultures are obtained from the catheter port or lumen, and no other source of infection (e.g., pneumonia, translocation of bowel microflora) is suspected. Quantitative blood cultures showing higher colony counts from a catheter lumen than from peripheral sites, or isolation of >15 colony forming units on the tip of a removed catheter by the semi-quantitative roll-plate technique [148] would also implicate an intravascular device as the source of bacteremia. The use of antimicrobial-impregnated catheters for short-term venous access (mean 17 days) in patients with hematological malignancies has been associated with lower rates of line colonization and catheter-related bloodstream infection [149], but these data cannot be generalized to the longer-term, tunneled catheters favored for induction-remission chemotherapy in the setting of acute leukemia and marrow transplantation.

Central venous line removal is not required for all cases of catheter-associated bacteremia. Infections due to coagulase-negative staphylococci can be treated with the catheter left in place [150,151], although there is a greater potential for bacteremic relapse with this practice (20% vs 3% with catheter removal) [152,153]. The majority of exit site infections not due to *Pseudomonas* spp. may also be treated with the catheter in situ [150]. In other circumstances where the intravenous device is implicated in the febrile neutropenic episode, it should be removed.

Most febrile neutropenic episodes and bacteremias, for which a source other than the intravascular device itself is suspected, can be managed without catheter removal [154]. If blood cultures remain persistently positive after 48 hours of effective therapy, removal of the catheter may be warranted [151].

Case presentation (continued)

On day + 32, just prior to planned hospital discharge, the patient was noted to have a low-grade fever (oral temperature 38°C) and to be complaining of right upper quadrant discomfort. An examination revealed a liver span of 14 cm. A liver function profile demonstrated a total bilirubin of 24 μmol/L, an aspartate transaminase (AST) of 34 IU/L, alanine transferase (ALT) of 54 IU/L, lactate dehydrogenase (LDH) of 203 IU/L, alkaline phosphatase (ALP) of 267 IU/L, and gamma glutamyl transferase (GGT) of 376 IU/L consistent with a cholestatic enzymopathy. A repeat infused CT scan of the abdomen demonstrated multiple radiolucencies present in the parenchyma of the liver and the spleen. A diagnosis of hepatosplenic fungal infection was suspected. Further blood cultures grew no pathogens and a chest CT demonstrated no evidence of nodular lesions or consolidation. Culture of an open biopsy of the liver failed to grow any microorganisms; however, a silver methenamine-stained preparation demonstrated the presence of budding yeasts consistent with invasive candidiasis. On the basis of this information, a diagnosis of chronic disseminated candidiasis infection – presumed to have developed while the patient was receiving fluconazole antifungal prophylaxis – was established.

Chronic disseminated candidiasis

Chronic disseminated candidiasis (CDC) manifests as a persistent or recrudescent febrile illness in an individual who has received broad-spectrum antibacterial therapy for a febrile neutropenic episode, and whose neutrophil count has recovered [155–158]. Colonization of the gastrointestinal tract by yeasts [9,159,160], and chemotherapy with high-dose cytarabine (with associated oral and gastrointestinal mucositis) [158, 161] were the earliest identified risk factors; prolonged neutropenia (>15 days), younger age, and fluoroquinolone prophylaxis are likely contributing factors [162]. Fluconazole prophylaxis, outside of the marrow transplant population, has no apparent impact on the risk for development of CDC [74,162]. There is often an associated fungemic episode, the median time to which is day + 15 [9] or later [162,163]; the median time to recognition of disseminated infection is day + 40, at which time the neutrophil counts have recovered [9]. The pathogenesis is presumed to involve translocation of opportunistic yeasts across a damaged gut epithelium [9,161], with seeding of the liver and spleen. Most of the cases are accounted for by *Candida* spp, with the relative proportions of *C. albicans* and non-albicans yeasts varying with the uptake of fluconazole prophylaxis [71,163,164].

The presenting signs and symptoms of chronic disseminated candidiasis include fever in 85% and abdominal pain in over 50% of cases, with a cholestatic enzymopathy (elevated serum ALP and GGT) [165]. The total bilirubin may also be elevated. Abdominal computed tomography remains the diagnostic modality of choice at many centers: a scan showing multiple hypodense lesions in the liver and spleen, some of which may have a "bull's eye" appearance [166], reinforces the presumptive diagnosis. Magnetic resonance imaging of the liver has demonstrated improved sensitivity, negative predictive value, and overall diagnostic accuracy for CDC when compared to CT scanning or ultrasonography [167,168], showing typical, round, well-demarcated lesions early on that are hyperintense on T2 imaging, and a characteristic evolution of those lesions over several weeks of effective therapy. Histopathologic examination of a liver biopsy remains the reference standard for diagnosis, and will show typical granulomatous changes, with fungal elements on methenamine silver or PAS staining. Cultures of the biopsy specimen are most often negative [162,169], but the combination of an appropriate history with suggestive laboratory, imaging, and histology results should be sufficient to make the diagnosis.

There are no prospective studies comparing response rates among the different regimens used to treat CDC. Amphotericin B deoxycholate, at a dose of 0.6 mg/kg per day, for a total dose of 1.5–2.0 g, is considered the mainstay of therapy. Approximately half of the members of an expert panel recommended adding flucytosine to the amphotericin B regimen [170] for the treatment of patients who are acutely ill with their CDC, notwithstanding the increased risk of

flucytosine-related marrow toxicity in this population. Based on case-report and case-series data, [171–173] it has been suggested [124] that patients who are stable, and who have not been heavily colonized or fungemic with a fluconazole-resistant species of *Candida* (*C. glabrata*, *C. krusei*), can be treated successfully with that triazole antifungal at doses of 6 mg/kg per day (approximately 400 mg per day in an average sized adult). The lipid-based formulations of amphotericin B [174,175], voriconazole [176], caspofungin [177], are also effective in the treatment of CDC. It is recommended that any treatment be continued until symptoms, laboratory and imaging markers have resolved, or the lesions have calcified, and that patients continue to receive antifungal therapy during subsequent antileukemic therapy [178]. For individuals with refractory disease, adjunctive therapy with gamma-interferon and granulocyte-macrophage colony stimulating factor may be of some benefit [179].

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CHAPTER 16
Infections in general surgery

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Surgical site infections

Case presentation 1

A previously healthy 17-year-old male underwent emergency appendectomy for perforated appendicitis. Perioperatively, he received intravenous gentamicin and metronidazole. Within 24 hours of surgery, he developed progressively severe, generalized abdominal and right flank pain. This was associated with nausea, anorexia, and diaphoresis. On examination, he appeared flushed. The heart rate was 140 per minute; blood pressure 100/40; respiratory rate 26 per minute; temperature 39.4°C. Abdomen was diffusely tender. Surgical wound site revealed areas of dusky discoloration, purulent discharge, and foul odor.

Postoperative site soft-tissue infections

It is estimated more than 40 million surgeries are performed each year in the United States [1]. Surgical site infections (SSI) are one of the most common types of infections among surgical patients and occur following 2–17.9% of operations [2,3]. This, however, is likely an underestimation as the postoperative length of hospital stay has decreased significantly over the past decade and several studies indicate that 50–84% of SSIs occur after hospital discharge [3–6].

SSIs are subclassified into *superficial incisional*, involving the skin and subcutaneous tissues; *deep incisional*, affecting the fascial and muscle layers of the incision, and *organ space*, which describes infections in any part of the organs or spaces other than the incision that was exposed during the procedure. Organ space infections include postoperative intraabdominal abscesses, empyema, or mediastinitis [7]. Management of organ space infections is predominantly surgical and is beyond the scope of this review. The SSI risk factors, burden on healthcare costs, associated morbidity, mortality, and preventive measures are well described in the literature.

Evaluation of postoperative patients with suspected infection

Fever is the most common symptom of postoperative infection. Fever occurs in approximately 30–40% of patients after a major operative procedure [8,9]. Fever during the first 3 days of the postoperative period is often due to a noninfectious cause: medications, atelectases, deep vein thrombosis, or injury to tissue [10]. In a retrospective review of patients undergoing major gynecologic surgery, Fanning et al. identified that 84% of patients, who were discharged despite experiencing fever of ⩾38.0°C, did not have a documented infectious etiology for the fever [8]. Presence of fever alone is not an indication for initiation of antibiotic therapy.

A postoperative patient with fever requires a systematic, complete evaluation. This includes careful, repeat history, complete physical examination, along with supportive laboratory tests, if indicated: complete blood count with differential, urinalysis, bacteriologic cultures of blood, tissue/aspirated fluid from surgical site. Selective imaging studies, particularly computed tomography of the abdomen and pelvis, may be useful in evaluating a patient with late-onset, postoperative fever, after an abdominal surgery,

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without an apparent source, in localizing occult infection or intraabdominal abscess. The common causes of nonsurgical site-related, postoperative infections and fever, which include urinary, respiratory tracts, and catheter-related infections can be readily delineated by meticulous assessment of the patient. The majority of SSIs occur 5 or more days after surgery but necrotizing soft tissue infections, particularly due to clostridial species or Group A streptococci can manifest within 36 hours after an operation [11].

If the clinical assessment establishes the diagnosis of surgical site infection, as indicated by presence of purulent discharge from the wound, then the treatment is to open the wound for drainage. To date, there are no RCTs which have compared drainage to conservative management. The next step is to determine whether further operative intervention is necessary. SSIs, with the exception of uncomplicated cellulitis, require mechanical procedures to open an infected wound, drain abscesses, and remove devitalized tissues. An empiric antibiotic therapy is warranted along with exploration of the wound if there is painful spreading erythema over the surgical incision site, suggestive of cellulitis, or accompanying fever of $\geqslant$38.0°C, tenderness, edema, and an extending margin of erythema at or around the surgical incision site.

A number of factors will influence the choice of empiric antimicrobial agent(s). These include patient-associated factors, including host immunity, presence of diabetes mellitus, and length of preoperative hospital stay; procedure-associated factors such as the type and duration of perioperative antimicrobial prophylaxis, and the duration of operation, class of surgical site [12]; and institution-specific factors such as the hospital's microbial antibiogram (antibiotic susceptibility profile). Many SSIs are polymicrobial, often including microbes resistant to antibiotics. *Staphylococcus aureus* is the most commonly isolated organism from SSIs, followed by *Streptococcus pyogenes*, *Escherichia coli*, other enterobacteriaceae and anaerobes [13,14]. Based on these data, the responsible pathogens and the antibiotic susceptibility can be postulated and appropriate antibiotic can be instituted until the culture results are available.

Diagnostic work-up recommendations include obtaining aerobic and anaerobic cultures from the site of infection prior to initiating antibiotic treatment. The rationale for obtaining culture is to identify the bacteria involved in the infection and to institute appropriate antibiotic therapy [15]. Cultures should be transported at room temperature to the laboratory in appropriate aerobic and anaerobic transport media within 2 hours of specimen collection. Deep aspirates or tissue cultures are superior to swab samples in providing clinically relevant results [16]. The results of culture and antibiotic susceptibility can aid in modifying the antibiotic regimen as treatment failure can occur in the presence of resistant organisms [17,18].

Postoperative necrotizing fasciitis

Case presentation 1 (continued)

The wound was completely exposed and packed with sterile dressings. The infectious diseases service was consulted. Recommendation was made to surgically explore the wound to rule out possible necrotizing fasciitis and the addition of intravenous cefazolin to the existing antibiotic regimen of gentamicin and metronidazole. Surgical exploration revealed infection tracking into transversalis fascia and internal oblique. Portions of the transversalis fascia were necrotic. Infected and necrotic materials were completely evacuated. A Jackson-Pratt drain was placed in the pelvis. Histopathology confirmed the diagnosis of necrotizing fasciitis. Culture of the tissue grew mixed facultative anaerobic and anaerobic intestinal organisms.

Necrotizing fasciitis is a rare but potentially life-threatening, soft-tissue infection and it encompasses two types based on the bacteriologic entities [19]. Type I is caused by anaerobic species, especially *B. fragilis* in combination with one or more facultative anaerobic organisms other than Group A streptococci. Type II is caused by Group A streptococci, alone or in combination with other bacteria, most commonly *Staphylococcus aureus*. It is useful to distinguish the two types of necrotizing fasciitis as the medical management of type II differs from type I, although there is no difference in surgical management between the two types. Postoperative necrotizing fasciitis, as with other necrotizing fasciitis, is usually an acute, rapidly extensive inflammatory process [20]. The affected area is initially exquisitely painful and tender and this

is associated with rapidly progressive erythema, and poorly demarcated edema. The course is followed by fever, hemodynamic instability, skin discoloration from erythema to violaceous-gray, bullae formation and crepitation may be present. By day 4 and 5 of onset, frank cutaneous gangrene develops. Owing to associated morbidity and mortality with delay in diagnosis and management, it is paramount to recognize and institute immediate operative intervention when necrotizing fasciitis is clinically suspected [21,22].

During the early stage, it may be difficult to clinically distinguish necrotizing fasciitis from cellulitis as the local features of the affected area can be nonspecific. Presence of severe systemic toxicity and fever while the cutaneous appearance is innocuous should alert the clinician of possible underlying necrotizing fasciitis. The diagnosis of necrotizing fasciitis is made at surgery and it is essential to extensively excise the affected skin and subcutaneous tissues beyond healthy fascia [20,22]. Post debridement, a patient with necrotizing fasciitis usually requires critical care support and at times repeated surgical debridement.

Empiric antibiotic therapy and intravenous fluid must be promptly administered as soon as the diagnosis of invasive soft-tissue infection is considered. Initially, the antimicrobial therapy should consist of a regimen which reliably targets streptococci, *S. aureus*, enterobacteriaceae, and anaerobic organisms. For type I necrotizing fasciitis, broad-spectrum antibiotic is continued as it is an infection due to mixed organisms. In type II necrotizing fasciitis, confirmed by detection of Group A streptococci, a combination of high-dose intravenous penicillin G and clindamycin is the treatment of choice [23–25]. Necrotizing fasciitis may be accompanied by streptococcal toxic shock syndrome (STSS), as evidenced by a blood pressure of 90 mmHg systolic or below and evidence of end-organ damage, including renal, liver, pulmonary (adult respiratory distress syndrome) impairment in addition to rash or necrosis. A comparative observational study by Kaul et al. [26] showed that intravenous immunoglobulin (IVIG) administration for STSS was associated with an increase in 30-day survival. Others have also described the successful use of IVIG in patients with STSS [27,28].

In summary, despite advances in surgical techniques and infection control practices SSIs continue to be common nosocomial infections. The basic principle of management of SSIs is to open the infected site and allow it to drain. Antibiotics have an adjunct role only when there is invasive infection. There is no guideline or study which specifically addresses the duration of antibiotic therapy for SSIs. The patient's overall clinical response to surgical and adjunct pharmacologic interventions should guide the duration and the route of antibiotic administration.

Mesh infections after incisional hernia repair

Case presentation 2

A 59-year-old woman presents with a 4-day history of purulent discharge from a previous abdominal surgical site, fever, and malaise. One month prior to this presentation, she underwent abdominal wall sarcoma resection, followed by insertion of polytetrafluoroethylene mesh and reconstruction of the abdominal wall. She has a temperature of 37.6°C, a blood pressure of 128/82 mmHg, a respiratory rate of 20 breaths per minute, a heart rate of 90 beats per minute, and oxygen saturation of 96% while breathing ambient air. Abdominal examination revealed erythema and induration over the right, lateral aspect of the abdomen. There were three small areas of opening with thick, purulent yellow secretion at the right lateral corner of the graft. The white blood cell count was 14.3×10^9/L. The skin and subcutaneous tissues are opened and the mesh was exposed. The patient was managed with surgical debridement and irrigation of the wound.

The culture of the wound grew Staphylococcus aureus, sensitive to methicillin. Intravenous cloxacillin 2 g was started and the surgeon sought your advice for further management of this patient.

Following an elective laparotomy, between 10% and 20% of patients develop incisional hernia [29]. Without prompt reduction and repair, there maybe serious complications, such as incarceration and strangulation of the small bowel [29–31]. The major risk factors for developing incisional hernia are obesity, malnutrition, wound infection, and reopened incisions [32]. After a primary repair, several studies

have found high rates of recurrent hernia, from 24% to 54%. A number of studies [33,34], including a multicenter randomized trial [29], indicated reduced relapse rates using prosthetic biomaterials compared to suture repair of the hernia.

Evidence to guide management of mesh infections is based on biologic principles and animal studies, as there are no cohort or randomized controlled trials. Polypropylene (Marlex, Bard Inc.) and polytetrafluoroethylene (Gore-Tex, WL Gore and Assoc. Inc.) are the most commonly used prosthetic biomaterials for ventral hernia repairs [34]. Compared to polypropylene mesh (PPM), polytetrafluoroethylene (PTFE) possesses significantly superior mechanical properties, which facilitate incorporation of the mesh into fibrocollagenous tissue and at the same time prevent permeation of water. PPM has been shown to cause extensive visceral adhesions and erosion of the skin or intestines with long-term use [35–37]. Two small animal studies addressed the role of PPM and PTFE use in repair of contaminated abdominal wall defects. Bleichrodt et al. [35] from the Netherlands studied 42 rats; PTFE patch were used on 21 rats to repair abdominal wall defects contaminated with bacteria and, similarly, 21 other rats received PPM mesh. Wound infection occurred in 16/21 rats in the PTFE and in 14/21 rats in the PPM group. Two rats in each group died as a result of ileus (1/4) or peritonitis (3/4). In contrast, Brown et al. [36] reported significantly fewer bacteria ($P < 0.05$) adhered to PTFE compared to PPM, in an experimental model using 100 guinea pigs with simulated abdominal wall defects in the presence of *Staphylococcus aureus*-related intraabdominal infection. Based on the above results and paucity of human studies, it appears that there is a lack of distinction between the two prosthetic biomaterials in repair of contaminated abdominal wall defects.

Contrary to common perception, there are no data to suggest that infection occurs more commonly with the use of mesh insertion, compared with conventional suture repair. The reported infection rates related to mesh use is 0.03–0.8%, and that of suture repair is 1.0–1.2% [38–41].

The immediate host response to mesh implantation is recruitment and infiltration of inflammatory cells. In an ideal milieu, acute inflammation is replaced by fibroblasts, multinucleated giant cells, leading to complete incorporation of deposited mesh into the neighboring tissues and induction of collagen synthesis [42,43]. When the inserted mesh is not properly taken up, complications such as accumulation of seromas (an excellent medium for bacterial growth), chronic sinus formation, fecal fistula, or mesh extrusion may occur [32,44–47]. In a study by Amid et al. [48] the majority of these complications were attributable to errors in surgical techniques, for example improper positioning of the mesh, inadequate fixation and use of unabsorbable sutures.

Surgical site infections occurring early in the postoperative phase are usually independent of mesh utilization. These infections are primarily limited to the skin or subcutaenous layers and do not appear to interfere with proper mesh incorporation into host tissues [32,43]. With administration of appropriate antibiotics, proper drainage, and debridement, it is rarely imperative to remove the mesh to eradicate the infection [40].

Deep prosthetic-related infections, on the other hand, usually occur several weeks to months after surgery and occur infrequently at a rate of 0.03–0.8% [38].

Mesh-related infections result in cardinal symptoms of inflammation with a wide spectrum of severity. The factors that determine clinical presentation include: virulence of the infecting pathogen, the nature of the host tissue and its ability to support microbial growth, and the host response to the presence of these pathogens. Most patients present with a subacute to indolent course, characterized by progressive, crescendo wound pain, occasionally accompanied by cutaneous draining sinuses. Fever, soft-tissue swelling, and erythema may be absent. Rarely, some may present with acute, fulminant sepsis with high-grade fever, severe pain over the surgical site and soft tissue swelling, erythema and exudates. The infecting organism in this acute form is typically virulent, such as *Staphylococcus aureus*, and it can elicit more systemic inflammatory responses compared to innocuous organisms, for example coagulase-negative staphylococci, *Bacillus* and *Corynebacterium* spp. β-Hemolytic streptococci and aerobic, enteric gram-negative bacilli are also capable of causing mesh-related infections and these pathogens can incite severe inflammatory reactions similar to *Staphylococcus aureus*.

Case presentation 2 (continued)

During the 2 weeks of local surgical site care and intravenous antibiotic therapy, the patient's signs and symptoms of systemic infection resolved. The abdominal surgical site was left open and she was discharged home with intravenous antibiotic and daily surgical site care by a visiting home-care nurse. One month following the hospital discharge, the patient presented with purulent, foul-smelling greenish suppuration from the abdominal wound and the exposed mesh. She is afebrile and hemodynamically stable. The surgical site culture grew Pseudomonas aeruginosa. At this time, you recommend removal of the infected mesh and the surgeon is reluctant to do so.

Based on the results from the combined European and American groups' observations, which included 12 374 cases of hernia repair using mesh, only eight patients developed mesh infection; five of the eight patients required removal of the mesh [49,50]. In a case report series consisting of three patients, the infections were completely eradicated in all the patients after the removal of the infected mesh [50]. Hence, based on these limited observational findings, it appears that patients who experience refractory infections despite repetitive drainage, lavage, and appropriate systemic antibiotic therapy may improve following removal of the prosthetic material. It is improbable that an adequately powered, prospective, randomized trial of conservative therapy versus surgical management for mesh infection will ever take place, given the very low rate of infectious complications and significant risks and morbidity associated with reoperation.

When a patient presents with infection, the decision and the timing of the mesh removal should be tailored to each patient, while considering the benefit and risks associated with repeat surgery in the individual patient. For patients who display evidence of persistent sepsis, while infected with virulent organisms, such as *S. aureus*, and aerobic, enteric gram-negative bacilli, immediate removal of the mesh is likely necessary.

In conclusion, although mesh-related infection is rare, it is a significant complication. The risk of infection can be minimized with strict adherence to aseptic techniques during mesh preparation and implantation, while conforming to current perioperative recommended guidelines for SSI prevention.

Acute diverticulitis

Case presentation 3

A 62-year-old woman with a history of diverticulosis and hypertension presented with a 3-day history of left lower quadrant pain, anorexia, low-grade fever, and chills. There was associated dysuria, urinary urgency, and frequency. On physical examination, blood pressure was 116/62 mmHg; heart rate, 110 beats per minute; temperature 38.2°C. The jugular venous pressure was 2 cm below the sternal angle and the mucous membranes were dry. There were normal bowel sounds, moderate tenderness, and rigidity in the left lower quadrant and suprapubic area. There was no costovertebral angle tenderness.

The white blood cell count was 16.7×10^9/L; hemoglobin 104 g/L; platelets 407×10^9/L. Routine biochemical tests and urinalysis were normal. A clinical diagnosis of diverticulitis was made. You admitted the patient for intravenous hydration and for consultation with a general surgeon. You searched the literature to determine optimal evidence-based diagnosis of diverticulitis.

Epidemiology

Acquired colonic diverticular disease is common in industrialized countries, where it is estimated to affect approximately 5–10% of individuals over 45 years of age and nearly 80% of the elderly over 85 [51]. There is a growing evidence that the overall prevalence is increasing and the incidence in patients under 40 years of age is 2–5% [52,53]. The increase in prevalence in younger patients seems to be without regard to a particular socioeconomic or ethnic group [54]. There is a male preponderance for younger patients compared to both sexes being equally affected in the elderly population [4].

Prior to a few decades ago, diverticular disease was exceedingly rare in developing countries and Japan, attributed largely to sufficient dietary fibre consumption [55]. Recent studies indicate its increasing incidence in Africa and Japan with the introduction of

westernized diet, which is high in refined carbohydrate and low in fiber [55,56].

Diverticulitis refers to inflammation of diverticulosis and approximately 15–20% of patients with diverticulosis will develop diverticulitis [57]. Up to 20% of patients with diverticulitis are less than 50 years old. There is no clear evidence that younger patients have more severe diverticulitis, as previously thought. There maybe delay in diagnosis due to the atypical age of presentation and subsequent development of complications [54].

Pathogenesis

Colonic diverticulosis occurs due to elevated intraluminal pressure and thinning of the colonic wall [58]. The weakening of the bowel leads to herniation of mucosa and submucosa. Diets high in refined carbohydrate and low in dietary fiber lead to diminished stool bulk, an increase in gastrointestinal transit time and subsequent increase in intraluminal pressure [59]. Diverticulitis ensues when fecal material or undigested food particles lodge in a diverticulum, which can cause obstruction of the diverticulum neck. This results in accumulation of mucus, bacterial overgrowth, and loss of blood supply to the already distended diverticulum. In the majority of cases, the outcome is a microscopic perforation and localized inflammatory process. Hinchey et al. created a useful method to classify inflammatory conditions associated with diverticulitis [60]. Stage I is defined as small, confined pericolonic abscesses, which can lead to larger paracolic abscesses (stage II). Stage III depicts generalized suppurative peritonitis and stage IV is fecal peritonitis. With recurrent episodes of inflammation, fibrosis and stricture of the colonic wall may emerge [61].

Diagnosis of acute diverticulitis

Clinical features

The most common symptom of acute diverticulitis is a gradual onset of constant lower abdominal pain, particularly in the left lower quadrant, as the descending and sigmoid colons are involved in 90% of the cases [62,63]. There may be associated changes in bowel habits, especially in the setting of partial bowel obstruction. Nonspecific symptoms such as anorexia, nausea, and vomiting may accompany abdominal pain. When there is involvement of the bowel segment near the bladder or presence of colovesical fistula then urinary urgency, frequency, or dysuria may occur [61]. No studies were identified which specifically addressed the diagnostic accuracy of the clinical examination for diverticulitis.

Profuse rectal bleeding is unusual in acute diverticulitis but microscopic fecal blood may be present. Often, low-grade fever, mild leukocytosis, and localized lower quadrant abdominal tenderness are found. Presence of peritonitis reflects perforation of peridiverticular abscess or diverticulum. Patients receiving corticosteroids may not reveal evidence of peritonitis despite extensive colonic inflammation or perforation.

Case presentation 3 (continued)

After reviewing the literature with regard to the role of diagnostic imaging studies in the acute setting of suspected diverticulitis, you decide that your patient required a computed tomography (CT). The CT of the abdomen and pelvis with water-soluble contrast reveals pericolic fat inflammation, multiple diverticula, thickening the of the bowel wall. There is also a 3 cm pelvic abscess.

Imaging studies

Since up to 12% of patients with acute diverticulitis may have free intraperitoneal air, it is important to include chest and abdominal radiographs in the initial management of patients presenting with a significant abdominal pain and possible underlying diverticulitis [64].

Helical computed tomography (CT) scans with water-soluble colonic contrast materials have been shown to be very useful in ascertaining the presence of acute diverticulitis, with a positive predictive value of 100% and a negative predictive value of 98% [51,62,63,65]. Owing to the high risk of perforation, colonoscopy and barium enema should be avoided in acute diverticulitis. CT scanning, on the other hand, appears safe and can be performed even in critically ill patients.

The modern multislice CT scans, which provide speed and high-resolution imaging, when performed with rectal, oral (water-soluble), and intravenous

contrast have shown to accurately delineate intraperitoneal and colonic diseases [66,67]. Ambrosetti et al. [68] prospectively evaluated 542 consecutive patients presenting with acute left colonic diverticultis with high-resolution CT scans and contrast enema. The authors found the sensitivity of CT to be 98%, compared with contrast enema at 92% ($P < 0.01$), using a reference standard, which included either test being positive, or pathologic evidence of diverticulitis in resected surgical tissue. In addition to superior performance compared to contrast enema (CE) in terms of sensitivity, CT, also correlated with CE, was found to have better capacity to grade the severity of the inflammation with statistically significant differences ($P < 0.02$). This and several studies support the use of CT in evaluating patients with an acute presentation compatible with underlying diverticulitis, who require hospitalization to confirm the diagnosis, to assess the severity of the inflammation and to further direct patient management [63,65,68,69].

Case presentation 3 (continued)

On day 3 of the admission, the patient developed sudden onset of diffuse abdominal pain and vomiting. On examination, she was pale and diaphoretic. There was generalized abdominal guarding and rebound tenderness. A plain film of the abdomen showed increased gas in small and large intestines.

Treatment of acute diverticulitis

Medical management

Approximately 85% of patients with a first attack of acute diverticulitis will respond to conservative management, which consists of intravenous fluid administration, bowel rest, and broad-spectrum antibiotic therapy for 7–10 days [52,71]. No RCTs were identified that have assessed the individual efficacy of these components. Patients with a mild, first episode of acute diverticulitis, who are able to maintain oral hydration, can be treated as outpatients and given oral antibiotics effective against intestinal bacteria, for example ciprofloxacin and metronidazole [51]. Evans [70] analyzed 198 patients admitted with acute sigmoid diverticulitis as confirmed by CT and physical examination. The daily maximum temperature and leukocyte count of the patients with prolonged stays were compared to the patients who were discharged within 4 days. The average maximum temperature and leukocyte count on admission were not statistically different between the two groups. After the first 24 hours of admission, however, there was a statistically significant difference in maximum temperature ($P = 0.004$) between the two groups. The leukocyte count also decreased significantly by hospital day 2 ($P = 0.003$). The author found that the patients with a significant decline in leukocyte count and maximum temperature over the first 48 hours of medical management were predictably discharged early on oral antibiotics. Patients failing to show improvement of leukocytosis and fever at 48 hours required prolonged hospital stays and/or surgery.

The majority of patients admitted to hospital with initial onset of acute diverticulitis will improve within 2–4 days with bowel rest, appropriate intravenous antibiotic, and fluid therapy. The antibiotic therapy should consist of a regimen which reliably targets colonic gram-negative and anaerobic organisms. Several randomized trials demonstrated no statistically significant difference in overall outcomes between various collated antibiotic regimens for intraabdominal infections: ciprofloxacin + metronidazole vs imipenem/cilastatin [71]; piperacillin/tazobactam vs cefotaxime + metronidazole [72]; ertapenem vs ceftriaxone + metronidazole [73]; cefoxitin and gentamacin + clindamycin [74]; piperacillin/tazobactam vs clindamycin + gentamicin [75].

After the resolution of the initial acute attack, patients should be counseled to consume dietary fiber regularly and be advised to undergo colonoscopy to rule out underlying colonic cancer. Approximately 5–15% of the patients treated with medical management will experience recurrent diverticulitis within 2 years [76].

Surgical management

Fifteen percent of patients presenting with acute diverticulitis will require either percutaneous drainage or surgical intervention [71]. Small abscesses (<5 cm in diameter) usually drain spontaneously because of the development of fistulae between colon and the abscess and they generally resolve with antibiotic treatment [77]. Abscesses that are 5–15 cm in diameter can be drained percutaneously under

radiologic guidance. With the administration of appropriate antibiotic therapy and adequate percutaneous drainage, patients in this group frequently improve within 72 hours, as indicated by reduction in pain and normalization of leukocytosis [61,78]. Some of the advantages of percutaneous drainage are rapid control of sepsis, avoidance of general anesthesia for open drainage, and obviating the potential need for a second operation to restore colon contiguity.

Laparotomy is required when abscesses cannot be drained percutaneously due to inaccessibility, mulitiloculation, or lack of clinical response. Resection with primary anastomosis is the operative procedure of choice in such situations, as well as for patients who require definitive surgery even after a successful medical management, unless there are prohibiting factors such as edematous intestinal ends or inadequate bowel preparation [51,61].

The absolute indications for immediate colonic resection are uncontrolled sepsis, visceral perforation, generalized peritonitis, or colonic obstruction [61]. A review of practices and a recent prospective randomized study by Zeitoun et al. [80] determined that primary resection is superior to secondary resection in the treatment of generalized peritonitis related to diverticulitis in terms of immediate mortality and morbidity. In the latter study, 105 patients with sigmoid diverticulitis and generalized peritonitis were randomized to undergo primary or secondary colonic resection. Primary resection resulted in fewer reoperations (2 of 55 vs 9 of 48, $P = 0.02$) and shorter hospital stay (median 15 vs 24 days, $P < 0.05$).

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CHAPTER 17

Infections in the thermally injured patient

Edward E. Tredget, Robert Rennie, Robert E. Burrell & Sarvesh Logsetty

Case presentation

A 37-year-old male pipe fitter was tightening pipes in a petrochemical refining facility when a pipe burst, spewing him with a hot water/liquid ethylene glycol solvent mixture over 40% of his total body surface area (TBSA) including his upper extremities, chest, abdomen, and back. On the burns unit, routine admission wound, nose, rectum, and throat cultures were performed. He was resuscitated with fluids and nutritional support was provided by enteral feeding commenced at 24 hours post burn according to a routine protocol. His wounds were treated with topical silver sulfadiazine cream and his dressing was changed daily in a Hubbard tank hydrotherapy facility. After 5 days in hospital he underwent debridement and split-thickness skin grafting to his upper extremities; 3 days later he became acutely confused, tachypneic, hypotensive (80/60 mmHg), and oliguric. The patient was treated empirically with piperacillin 4 g intravenously every 8 hours and gentamicin 350 mg daily. His blood cultures grew *Pseudomonas aeruginosa* in both vials and methicillin-susceptible *Staphylococcus aureus* and *Enterococcus faecium* in one of two vials. The antibiotics were switched to amikacin 1 g daily, ceftazidime 2 g every 8 hours, and vancomycin 1 g every 12 hours. He required massive fluid resuscitation with crystalloids, fresh frozen plasma, and albumin totaling 35 liters over 30 hours as well as intravenous vasopressors, initially dopamine and dobutamine, but ultimately noradrenalin before he was stabilized and his urine output recovered.

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Serious infections remain a common complication in thermally injured patients, contributing substantially to burn morbidity and mortality. Despite advancements in medical and surgical care of burns patients, no significant improvement in mortality has been documented over a 25-year period in one major institution caring for burns patients once bacteremic with *Pseudomonas aeruginosa* [1]. Much of the evidence guiding management of infections in thermally injured patients is based on case series where bacteriologic results have been reported. Therefore a review of the bacteriology of burns is essential to understanding the evidence base for current practice.

Bacteriology of burns patients

The types of bacteria that colonize and infect burns patients, as well as their susceptibilities to antimicrobials, is highly variable between burns units. It is influenced by both the topical antimicrobial and wound care policies of the burns center as well as the approach to usage of systemic antibiotics. In India, Revathi et al. reviewed their experience with 600 infections in burns patients [2] and, similar to many burns centers, found that the most frequent and severe infections were caused by *Pseudomonas* spp followed by *Staphylococcus aureus* and then by other gram-negative organisms including *Klebsiella* spp., *Acinetobacter* spp., *Escherichia coli*, *Enterococcus faecalis*, and *Proteus* sp. In a survey of 176 burn care centers in North America, *P. aeruginosa* was considered the most serious cause of life-threatening infections in thermally injured patients [3]. Similarly, in a 25-year review of *Pseudomonas* bacteremia in burns patients by McManus et al., an overall burn mortality of 77% with *P. aeruginosa* bacteremia was documented, 28% above predicted rates [1].

A comparison of two 10-year periods of gram-negative isolates in pediatric burns patients demonstrated that, in the 1990s, *P. aeruginosa* accounted for 35% of the gram-negative organisms from all sites of infections, as compared with 34% in the 1980s. Most recently, however, *Acinetobacter* spp. have replaced *Klebsiella* spp. as the second most common gram-negative bacteria causing infections in children with burns [4]. Similarly, in an overview of wound isolates in burns centers in the United Kingdom, an increasing prevalence of *Acinetobacter* spp. has been described [5]. It is important to note that *Aeromonas* sp. is an uncommon, but rapidly aggressive gram-negative burn wound pathogen that can lead to early burn wound sepsis (within the first burn week) commonly after patients have been exposed to lake or slough water post injury [6].

In a large case series of established infections in the US army burns center, Pruitt et al. reported that 25% of infections were due to pneumonia, 22% to urinary tract, 26% to primary blood stream infections, and 5% to invasion of the burn wound [7]. Of the 57 documented cases of invasive wound infection that occurred in burns patients treated during the 1986–95 period, there were 26 cases of secondary bacteremia due to *P. aeruginosa*. In this major academic American military burns center where early burn wound excision, avoidance of immersion hydrotherapy, dependence on quantitative and histologic evidence for burn wound infection, and topical sulfamyalon are routine practices, a high rate of yeast and fungal infections occurred in burns of 50% or more of the total body surface area. Most of these fungal infections were in massive burn injuries and were due to *Candida* spp., which on average, colonized the burn wound on post-burn day 30, infected the urinary tract on day 48, and other sites at day 41 [7]. Filamentous fungi such as *Aspergillus* spp. and *Fusarium* spp. have also been reported to cause invasive infection [8]. Predisposition of burns patients to fungal infections has been identified when strong dependence on topical mafenide acetate solutions is used to control gram-negative bacteria in the burn wound [9].

Diagnosis

Clinical presentation

Approximately 400 000 cases of sepsis occur in the US each year with 30–45% mortality [10]. The clinical spectrum of burns patients resembles that of other septic patients [11]. Fever and inflammation following a burn injury is a very common response to localized microbial invasion to the burn wound. However, when the size of the burn increases beyond 15–20% of the total body surface area, release of cytokines and eicosanoid mediators leads to a systemic inflammatory response syndrome (SIRS), in the presence or the absence of a definable bacteriologic infection [11]. With progressive bacterial or fungal colonization of the burn wound, sepsis progressing to multiple organ dysfunction syndrome (MODS) and septic shock may occur. There are, to date, no clinical features that have been found distinguishing a burns patient with SIRS from a septic burns patient without hypotension. A thorough physical examination and septic work-up (blood, wound, and urine cultures; chest radiograph, and urinalysis) is necessary for the initial investigation of the burns patient with symptoms and signs of infection [12].

Evaluation of infected thermally injured patients is a challenge for clinicians. The clinical presentation of infection can range from an acute (such as the patient presented) to a chronic onset. This may range from low-grade cellulitis or minor skin graft infection to fulminant septic shock and widespread infection of skin graft donor site wounds and complete non-take of split-thickness skin grafts in the postoperative period [7]. Classically, bacterial colonization of the burn wound and eschar leads to progressive increases in the numbers of bacteria and penetration of the eschar from superficial to deep into the eschar before invasion into healthy uninjured tissue leads to bacteremia and sepsis [7]. Altered mental status, tachypnea, paralytic ileus, hyper- or hypothermia ($>$38.5°C or $<$36.5°C), hypotension and oliguria, associated with leukocytosis $>15.0 \times 10^3$ cells/mm^3 or leukopenia $<3.5 \times 10^3$ cells/mm^3, thrombocytopenia $<$50 000 platelets/mm^3, hyperglycemia, and unexplained acidosis are cardinal signs of burn wound sepsis [7]. Local evidence of invasive wound infection includes black or brown patches of wound discoloration, rapid eschar separation, conversion of partial thickness wounds to full thickness injuries, spreading peri-wound erythema, punctate hemorrhagic, subeschar lesions, and, with *P. aeruginosa*, violaceous or black lesions in unburned tissue termed "ecthyma gangrenosum" [13].

Microbiology cultures

Commonly, wound infection is diagnosed clinically and wound swabs of potentially contaminated tissues are obtained. Surface wound cultures are considered only partially representative of the bacterial flora contained within the wound [14]. For this reason, burn wound biopsies have been employed by many burn care centers to allow quantitation of the numbers of bacteria present within the wound where $>10^5$ organisms/g of wet tissue is considered evidence of wound infection, which will prevent successful wound closure surgically [14]. Recently, Steer et al. used parallel cultures from 141 samples in 74 burns patients to demonstrate that recovery of the same set of species of bacteria from a burn wound biopsy versus a surface swab was 54%, and the predictive value of the counts obtained by one method to predict the counts obtained by the other was poor, owing, in part, to wide variation in bacterial densities from simultaneous cultures taken from the same burn wound [14]. Further, in burns >15% TBSA, quantitative bacteriology by burn wound biopsy or surface swab did not aid in the prediction of sepsis or graft loss [14]. By definition, burn wound invasion leading to bacteremia is a histologic diagnosis where microscopic evidence of invasion of nonburned tissue with bacteria occurs, a finding which McManus found was present in only 36% of biopsies with positive cultures ($>10^5$ organisms/g) [15]. Unfortunately, burn wound biopsies are expensive, invasive because a section of unburned tissue needs to be included with the biopsy, and associated with considerable variability between adjacent sites of the burn wound [16]. These facts together with more aggressive wound debridement, newer topical antimicrobials, and improved nutritional support and intensive care have limited the use of burn wound biopsy in many burns centers [17].

Laboratory diagnosis of infection in the burns patient also includes blood cultures, urine and respiratory cultures, depending on clinical clues such as sepsis, pyuria, and evidence of pulmonary infiltrates.

To date, there is little evidence to support the routine use of blood culture testing in burns patients. Keen et al. in a small retrospective analysis of 47 burns patients found that positive blood cultures were more common in patients who were in shock, had larger burn wounds, were receiving more antibiotics, and who had indwelling catheters [18]. Reduced frequency of blood cultures was not associated with increased length of stay, ventilator days, or mortality [18]. The small size of this study, however, probably precludes the ability to detect differences. Henke et al. conducted a retrospective analysis of 1040 routine blood cultures in 121 surgical patients (including 31 burns patients) [19]: 48 positive blood cultures led to a change in management or therapy in 19 (40%). Of interest is the fact that the mortality rate was highest in burns patients who had positive blood cultures (39%) as compared with those with negative blood cultures (7%) [19].

It is routine practice for many burns units to perform cultures of the burn wounds, throat, nose, and rectum upon admission to identify any unusual or high-risk pathogens. However, there are no data to support this practice. Although many burns centers perform routine weekly cultures on patients with open wounds, there is little evidence to support routine wound cultures and the practice is expensive and timeconsuming [20]. In addition, considerable data suggest that surface swabs of burns and other wounds are often not representative of the major bacteria present in the wound [14–19] and therefore quantitative burn wound biopsy and histology, with their inherent limitations as discussed earlier, is employed in many but not all burns centers.

Prevention of infection

Topical antimicrobials

The burn eschar is a relatively avascular mass of necrotic material in which therapeutic levels of systemically administered antibiotics are difficult to achieve [21]. Topically applied antimicrobials provide high concentrations of drug at the wound surface acting as a barrier to infection and penetrate the eschar to varying extents, significantly delaying the onset of invasive infection [22]. Much of the evidence on the use of topical antimicrobials in thermally injured patients is based on small clinical trials that used bacteriologic primary outcomes or bacteriologic considerations alone. Choice of topical agents often also depends on ease of use and other treatment modalities being offered to burns patients.

Silve sulfadiazine

Silver sulfadiazine is synthesized from silver nitrate and sodium sulfadiazine and is easily applied to

burn wounds and does not stain the environment. Although this used to be a common prophylactic topical agent in burns patients, its white, water-soluble cream base interacts with the wound to produce a yellow mucopurulent exudate that needs to be washed off the wound before reapplication every 12 hours as recommended by the supplier [23]. Clinical experience suggests that silver sulfadiazine reduces wound bacterial density and delays colonization with gram-negative organisms but that treatment failures occur frequently in large burns >50% TBSA [24]. Because this agent is of limited spectrum in the large burn and requires hydrotherapy, which is an established risk factor for nosocomial infections, its usefulness in established *Pseudomonas* infections appears to be low, and its use combined with hydrotherapy predisposes major burns patients to early *Pseudomonas* colonization of the burn wound. Systemic absorption and multi-organ toxicity of silver is high in major burns, often unrecognized, and severe in patients with compromised renal function, the kidney being the principal route of excretion of absorbed silver [25].

Silver nitrate

Historically, **silver nitrate** was the first topical agent employed to delay burn eschar colonization based on its effectiveness against most strains of *Pseudomonas* and *Staphylococcus*. New topical agents were then developed to improve on the limitations of silver nitrate, including limited penetration of the burn eschar and environmental staining [26]. However, there has been a resurgence in the use of silver nitrate based on the recognition that, as a solution, it avoids the mucopurulent exudate common with cream-based topicals, and therefore does not require hydrotherapy. In addition, with the use of new skin and dermal substitutes, topical therapy without hydrotherapy is imperative and effective. Finally, eliminating the use of hydrotherapy not only reduces the risk of nosocomial infection (as discussed below) [27], it reduces the frequency of dressing change to once per day, significantly decreasing the dressing-related pain and cold stress endured by patients during hydrotherapy sessions, and also substantially lowers the overall cost of care of both the topical agents required but primarily of the staffing required for twice daily wound care and hydrotherapy sessions [3,27].

Mafenide acetate

Mafenide acetate is a topical burns agent with activity primarily against gram-negative organisms including *Pseudomonas* [24], where its efficacy has been established in vivo based on the Walker burns model in rats, where both topical 5% mafenide acetate solution and 10% cream significantly reduced *Pseudomonas* colonization to <10% organisms/g over 48 hours in standardized full-thickness burns [28]. Using ^{14}C-labeled mafenide acetate, Harrison demonstrated rapid penetration of this topical antimicrobial through burned skin [29]. It has minimal antifungal activity and limited activity against *Staphylococcus aureus*, particularly methicillin-resistant strains. It is formulated as an 11.1% cream or more recently as a 5% solution [28]. Mafenide is a potent carbonic anhydrase inhibitor; hyperchloremic metabolic acidosis limits its application to <20% TBSA; otherwise, severe hyperventilation can develop as respiratory compensation for the metabolic acidosis. For established *Pseudomonas* infections, mafenide acetate solutions can be combined with nystatin for improved antifungal activity and effectiveness in serious infections; it is often alternated every 12 hours with 0·5% $AgNO_3$ or other topical agents [30].

Acticoat

Acticoat is a new topical agent that is a novel nanocrystalline silver complex that has been widely tested and effective in vitro against a broad range of gram-negative and gram-positive organisms including multiply resistant strains [31–33], and it possesses strong antifungal properties [30]. It releases silver in aqueous solutions and therefore must be moistened with sterile water for activity, but thereafter can be left in place for up to 72 hours; it also does not normally require hydrotherapy for wound cleansing before reapplication [17]. In vivo studies have been completed on the antimicrobial barrier properties of the Acticoat dressing [34] as well as on the healing rates of skin graft donor sites [35] and contaminated full-thickness burn wounds [36]. One small randomized controlled trial in patients with major burns suggests that Acticoat treatment may be associated with lower rates of burn wound sepsis and fewer secondary bacteremias [27]. Using a matched pairs design of patients with symmetric wounds, one wound in each of 15 pairs was randomized to receive Acticoat, the

other standard therapy (0.5% silver nitrate solution). Five cases of burn wound sepsis based on quantitative wound biopsy cultures ($>10^5$ organisms per gram of tissue), associated with one secondary bacteremia were noted in the Acticoat group compared with 16 positive wound biopsies and five secondary bacteremias with silver nitrate standard therapy. Other small uncontrolled clinical trials have been supportive of its use in burn wounds [37,38].

Other topical agents

Other topical agents for wound care include nitrofurazone, chlorhexidine, providone-iodine, nystatin, cerium nitrate, and combinations of agents, but are of limited proven efficacy and safety in *Pseudomonas* infections as yet [24]. Similarly, infusion of antibiotics under the burn eschar, termed "subeschar lysis," has been performed but has not yet been tested in randomized controlled trials [39].

Surgery

Prompt surgical excision of the burn wound and timely closure have significantly reduced the occurrence of invasive burn wound infection and its related mortality; however, as wound closure is delayed in patients with massive burns, the potential of invasive wound infection remains [40]. Two randomized controlled trials have reported no survival advantage with early total excision as compared with conservative treatment commencing at the day 10–14 post burn [41,42]. However, Tompkins et al. reviewed mortality in adult burns patients from Massachusetts General Hospital during a period prior to early excision and after prompt eschar excision and immediate wound closure. Using logistic regression of 1103 patients over a 10-year period encompassing both surgical approaches, the data showed a reduction in mortality from 24% to 7% ($P < 0.001$) associated with a significant reduction in length of stay in hospital from 32 to 22 days [42]. Staged surgical wound closure beginning within 10 days of injury and continuing at 7-day intervals remains the most common surgical approach to the burn wound at present [41]. The supporting evidence for this approach is limited to observational studies. In one study, this approach was associated with a 6-fold reduction in mortality in patients with burns >50% TBSA, with delayed surgical excision commencing after 7–10 days post injury [43]. In a single-center retrospective analysis of 3561 burns patients over a 14-year period, Munster et al. reported significant reductions in mortality, length of stay, and cost of care with more aggressive staged surgical excision of the burn wound in the later 7-year period compared with the early era [41]. However, comparison with historical cohorts is a substantial limitation of the study [1]. Large, adequately powered randomized controlled trials are needed to establish optimal timing of surgery. In patients who already have established *Pseudomonas* infection including ecthyma gangrenosum, surgical debridement of infected tissues and temporary wound closure with allograft skin or autograft once the patient has stabilized is considered crucial to survival [13,44,45].

Empiric antibiotic treatment

Unstable septic patients often require empiric therapy usually guided by initial cultures taken on admission. Initial antibiotic therapy is based on these swabs and tailored once further cultures and susceptibilities become available. Leibovici et al. surveyed 296 episodes of gram-negative bacteremia in 286 patients aged 13–99 years and found that thermal trauma, hospital acquisition of the infection, antibiotic treatment before the bacteremic episode, and endotracheal intubation were variables that independently predicted subsequent isolation of a multiresistant strain [46]. In a second group of 144 episodes of gram-negative bacteremia, the predictive index derived from these variables for optimizing empiric treatment maintained good discriminative power and improved empiric antibiotic treatment in 24% of patients [46].

Pseudomonal sepsis is a significant cause of burn-associated mortality and morbidity requiring systemic antimicrobial therapy. McManus found that 10% of all burns patients developed pseudomonal bacteremia [1]. Unfortunately, with the development of multidrug-resistant *Pseudomonas*, the choice of antibiotics for empiric therapy becomes more difficult.

Case presentation (continued)

Septic work-up cultures in the unstable burns patient were positive for *P. aeruginosa*, which was quantified

Continued

Case presentation (continued)

in burn wound biopsies $>10^8$ organisms per gram of tissue, and skin graft donor sites from multiple regions of the body including his chest, back, both lower extremities, face, and scalp, as well as his blood cultures. The organism was resistant to gentamicin, tobramycin, carboxy- and ureidopenicillins. The patient's topical antimicrobial therapy for all infected wounds was switched to mafenide acetate twice daily. Once hemodynamically stable, the patient underwent a series of seven surgical debridements under general anesthetic for infected burn wounds and donor sites, but also for other infected wounds, which were not in the original burn areas but were hematogenously disseminated wounds in the scalp and other areas in which *Pseudomonas* was recovered on culture of the debrided tissue. Early surgical procedures were directed at debridement of *Pseudomonas*-infected tissues and avoidance of creation of any new skin graft donor wounds until reduction of bacterial load had been achieved, evidenced by adherence of fresh allograft skin to the debrided wounds. Despite secondary urine and wound infection with *Candida albicans*, the patient recovered after 77 days of intensive care in the burns unit. He spent 2 months in a rehabilitation hospital before being able to return home; he recommenced his work approximately 1 year after his original injury.

Infection control

Pseudomonas aeruginosa is the most important cause of nosocomial infection in the burns patient. However, only 6–8% of burns patients have rectal colonization [27]. Nosocomial acquisition of *P. aeruginosa* and other gram-negative bacteria arises from contaminated water and aqueous solutions used in Hubbard tanks, ventilators, nebulizers, intravenous solutions, and hemodialysis systems [47]. During wound care, hand-to-hand transmission is considered to be the major preventable mode of transmission.

Both the experimental and observational evidence to support infection control interventions in burns units are extremely limited. Strict handwashing is considered the cornerstone in preventing transmission of antibiotic-resistant organisms. Ongoing surveillance of infections in the burns unit is important to defect new resistant organisms so that infection control precautions can be quickly instituted [48]. Isolation and performing admission swabs for culture of new patients can potentially identify new pathogens, especially those from patients who have received care in another institution [49]. However, there are no comparative studies at present that have validated this. Strict barrier precautions are used in many burns units. On entry into the burns patient's room, all personnel and visitors are required to wear a disposable gown and mask and to wash their hands [50]. For all direct contact with patients sterile gloves are worn. Hands are washed with an antibacterial soap or alcohol-based hand disinfectants, and all protective garments are changed after each patient encounter. Individualized rooms and beds are cleansed and walls washed with a quaternary ammonium disinfectant between patient admissions. Again, however, comparative evidence for various levels of barrier precautions in burns units and terminal cleaning are lacking.

Improperly designed sinks that have short trap drains and deficient splash guards in themselves can be a source of hand and subsequently wound contamination [51,52]. This is very difficult to detect and establish as a mechanism of transmission of nosocomial infection but has been reported [53–55] and corrected by redesign and implementation of appropriate facilities for safe handwashing. Each individual piece of equipment is soaked with full strength (12%) sodium hypochlorite solution if positive surveillance cultures are obtained [1].

Selective decontamination of the gastrointestinal flora of the burns patient has been tried without success to reduce burn wound infection by either direct contact or by bacterial translocation of organisms from the gut [56]. Small numbers of burns patients treated with selective gut decontamination compared with historical controls found lower but not significantly reduced rates of wound colonization and respiratory infection, but a subsequent prospective randomized double-blind study of 23 pediatric burns patients demonstrated comparable rates of colonization and infection as compared with the blinded placebo controls [57].

The role of hydrotherapy in burn wound management

There are no randomized controlled trials that have compared hydrotherapy to no hydrotherapy for burn wound management and its use appears to have

developed from a practical desire to wash burn wounds and the need to remove topical antimicrobial creams prior to reapplication of fresh agents. However, observational data of harm related to this therapy exists. Following an outbreak of *P. aeruginosa* linked to hydrotherapy in one burns unit, the incidence of *P. aeruginosa* infections in equal periods of time before and after discontinuation of hydrotherapy was compared [27]. Demographic data showed no difference in burn size, age of patient, duration of hospitalization, or sample size. However, a significant reduction in overall mortality (14 vs 6, $P < 0.05$), septic mortality (8 vs 1, $P < 0.05$), and *Pseudomonas*-associated septic deaths (6 vs 0, $P < 0.05$) was found in the non-hydrotherapy group. There was a significant reduction in the nosocomially acquired organisms (29 vs 18, $P < 0.05$), and in the number of aminoglycoside-resistant strains of *Pseudomonas* sp. (20 vs 4, $P < 0.05$) in the non-hydrotherapy group. Avoidance of hydrotherapy was also associated with a delay in appearance of *Pseudomonas* sp. in the burn wound (10.1 vs 16.5 days) and a delay in the onset of aminoglycoside resistance (10.3 vs 19.5 days), such that the appearance of an aminoglycoside-resistant organism in the burns patient was delayed approximately 16 days longer in the nonhydrotherapy group (20.4 vs 36.0 days) [27]. During the post-hydrotherapy period, an elimination of *Pseudomonas* sp. infection from traditionally clean wounds of the skin graft donor site was achieved (5 or 2.3% vs 0, $P < 0.05$). During the period prior to and after discontinuing hydrotherapy, the cost of care for patients in this burns unit was also analyzed where, from 1987 to 1991, silver sulfadiazine cream and hydrotherapy was routine before hydrotherapy was discontinued and topical 0.5% silver nitrate solution was substituted [58]. By using mathematical modeling to control for the number of burns patients and severity of injury during each period, substantial reduction in overall costs were predicted and savings in excess of the predicted were actually achieved. The majority of reduction in cost of care was not in the expense of the topical antimicrobials employed for wound care (Can$29 623 vs Can$10 145 per month), but in the reduced labor/nursing costs ($112 046 vs $91 256 per month) associated with elimination of hydrotherapy and once daily dressings within the patient's isolation room. An important limitation of this study, however, is the use of an historical cohort for comparison.

Similarly, many burns centers are experiencing an increase in *Acinetobacter* infections that are nosocomial in origin. Wisplinghoff et al. demonstrated that, in 367 patients hospitalized with severe burn injury where *Acinetobacter baumannii* was endemic (attack rate of 7.9%), 29 patients developed bloodstream infections [59]. When compared with 58 noninfected matched controls, the mortality rates were 31% and 14% respectively, and two deaths were directly attributable to *Acinetobacter* infections. Pulsed-field gel electrophoresis demonstrated three common strains, which were multidrug resistant. Multivariate analysis showed that bloodstream infection was independently associated with the severity of burn injury, prior nosocomial colonization at a distant site, and the use of hydrotherapy, again emphasizing the importance of effective infection control in other types of gram-negative infections. In summary, there are no trials that establish the efficacy or benefit of hydrotherapy for burn wounds. However, the substantial risk of cross-contamination of multidrug-resistant bacteria owing to hydrotherapy is well documented. This has led many burns centers to avoid using immersion hydrotherapy [4].

Prognosis

Based on retrospective, multifactorial logistic regression and probit analysis of 1705 burns patients, the mortality and morbidity of burns patients is related to the age of the patient, the total area of the burn wound (TBSA), and the presence or absence of concomitant inhalation injury [43], which resemble the findings of other burns centers [60]. Measures of the severity of injury after burns injury such as burn surface areas are often only broad, insensitive predictors of outcome. This is because of the failure to recognize the importance of inhalation injury and the depth of burn as a reflection of the volume or magnitude of necrotic tissue [61]. For example, superficial sun burns over 90% of the TBSA without inhalation injury can be considered in the same category of severity as full-thickness flame burns after a house fire, where the same TBSA is recorded but the patient also sustained a significant inhalation injury. Despite these limitations, predictive equations derived from one burns center would suggest that the illustrated index case would have a 75% probability of survival,

where the total burn surface area, age of the patient, and presence or absence of inhalation injury are independent variables [43].

Inhalation injury and or adult respiratory distress syndrome (ARDS) and sepsis, ranging from SIRS to frank septic shock, are the major causes of mortality in burns patients [62]. Surveys from burns centers identify gram-positive organisms including MRSA as the most frequent cause of burn wound and skin graft infection [63]. However, the evidence suggests that gram-negative bacteria including *K. pneumoniae*, *E. coli*, and *Acinetobacter* spp. as well as *P. aeruginosa* are the major causes of mortality in burns centers. McManus et al. reported that 10% of all burns patients develop *Pseudomonas* bacteremia, carrying a mortality rate of 80% [1,64]. The risk of *Pseudomonas* infection increases substantially in burns >30% of the TBSA.

Emerging data for major burns involving more than 30–35% of the TBSA suggests that they do not necessarily all become infected with *P. aeruginosa* [65]. However, *Pseudomonas* morbidity and mortality may be reduced by measures taken to avoid nosocomial infection or to delay the onset of infection as long as possible [27]. One study of burns patients, using historical controls, suggested that the delay in the onset of resistant infections led to a 9-day or more infection-free period, enough time for surgical procedures to remove potentially infected burns tissue and close wounds with skin grafts [27]. McManus et al. reported similar findings after moving into a new burns center and avoiding transmission of an endemic strain of *Pseudomonas* in the old center by cohort nursing and avoidance of moving patients from the old burns center into the new center [64].

Avoidance of nosocomial *Pseudomonas* infections is most important for patients with larger or deeper wounds, or in those who are older, have inhalation or other risk factors that put them at high risk of death from burn injury [1]. Recently, a review of mortality in burns >50% TBSA demonstrated a 6-fold lower risk of death when a setting with better control of nosocomial infection [51] was compared with historic controls in the same setting at a time when nosocomial infections were more common, and shared practices, facilities, or equipment for wound care (such as hydrotherapy) occurred. Recent improvements in outcomes may be due to additional factors such as earlier surgical care, newer skin substitutes, or better intensive care. However, reports exist where these factors did not significantly improve outcomes over a similar time period [60]. To date, a number of other reports of nosocomial *Pseudomonas* outbreaks in other burns centers have emerged resembling that described herein, where mortality was very high in the infected patients [47,66–69].

In burns centers that use silver nitrate as a topical agent for the burn wounds, thus avoiding hydrotherapy and maintaining high levels of reverse isolation in laminar flow units, the cross-contamination rate with multidrug-resistant organisms is extremely low, 3.2 cases per 1000 patient-days [70]. Other centers where similar isolation is not possible have demonstrated that 74% of burns patients wounds become colonized with *P. aeruginosa*, >95% of which are resistant to multiple antibiotics including gentamicin, when only 4.75% of patients are contaminated at the time of admission [71]. Such dramatic differences in infection rates between burns centers illustrate the broad range of treatment approaches practiced and the difficulty and deficiency of clinical trials addressing isolation procedures and antimicrobial therapy in burns centers.

New preventive strategies: vaccines

The serious nature of infections caused by *P. aeruginosa* has led to concerted efforts by many investigators to develop candidate vaccines for prevention of *Pseudomonas* infections in the burned patient and in persons with cystic fibrosis. Lipolysaccharide (LPS) vaccines conjugated to carriers have been produced. While they showed good immunogenicity in human trials, toxicity from the lipid A portion of the LPS has prevented their use [72,73]. Whilst there have been some studies with flagellar vaccines, their efficacy in humans has not been clearly identified [74,75]. Recently, outer membrane proteins (OMPs) have also been used as targets for *P. aeruginosa* vaccines. In human volunteers, recombinant OMPs expressed in *E. coli* showed good immunogenicity [76,77]. In one recent study in burns patients, a composite OMP vaccine showed promise in reduction of sepsis caused by *P. aeruginosa* [78]. Peptide vaccines are also being investigated. They have been derived from OMPs [79,80] or are being produced synthetically

as consensus sequences from pilin proteins [81,82]. These compounds may be conjugated to other proteins (e.g., tetanus toxoid) as haptens, to improve their immunogenicity. These consensus sequence peptides are strongly immunogenic in animal models, and are now undergoing phase I human clinical trials. It is still unknown if any of these candidate vaccine molecules will come into routine clinical use. It has been observed that the immune response following thermal injury may not be optimal [83] and therefore immunogenicity of these vaccines in animals or in healthy persons may not translate into efficacy in the burned patient.

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CHAPTER 18
Infections in healthcare workers

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Case presentation 1

A phlebotomist presents to you with a needlestick injury from a patient known to have advanced HIV and hepatitis C infections. She used the needle to draw blood and injected a small amount of blood into her finger accidentally while re-sheathing the needle before disposal. She is fully vaccinated against hepatitis B and had her antibody levels checked within the last 6 months. You counsel her about the risk of transmission of HIV and hepatitis C.

Occupational bloodborne pathogen exposures

It is estimated that American healthcare workers (HCWs) suffer between 300 000 and 460 000 needlesticks and other sharps injuries every year [1]. The American Hospital Association estimates that one case of infection by a bloodborne pathogen can incur expenditures of $1 million or more for clinical care and lost productivity. The cost of follow-up for a high-risk bloodborne pathogen exposure is almost $3000, even when no infection occurs [2]. The World Health Organization estimates that bloodborne pathogen exposures among HCWs are responsible for 66 000 cases of hepatitis B, 16 000 cases of hepatitis C, and 200–5000 cases of human immunodeficiency virus (HIV) annually, as well as a smaller number of other infections such as tuberculosis or malaria [3].

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HIV: infection and risk assessment

A summary of 25 case–control studies (22 seroconversions in 6955 exposed people) found that the risk of HIV transmission after percutaneous exposure was 0.32% (95% confidence interval [CI] 0.18–0.45%) and the risk after mucocutaneous exposure was 0.03% (95% CI 0.006–0.19%) [4]. However, the risk of transmission is higher following certain percutaneous exposures [5] (Table 18.1).

A recent Cochrane review [6] identified no randomized controlled trials on the effect of postexposure prophylaxis (PEP) on HIV transmission following occupational exposure. The only case–control study that was included in this review compared HCWs who acquired HIV infection after percutaneous exposure with HCWs who remained HIV-seronegative at least 6 months following occupational exposure [5]. After controlling for risk factors for seroconversion (Table 18.1), HIV infection was 81% less likely in HCWs who received postexposure zidovudine compared with those who did not (95% CI 43–94%). Efficacy of PEP following occupational exposures is

Table 18.1 Risk factors for HIV seroconversion after percutaneous exposure to a known HIV-infected source

	Adjusted odds ratio	95% CI
Deep injury	15	6.0–41
Visible blood on device	6.2	2.2–21
Procedure involving a needle placed in source patient's blood vessel	4.3	1.7–12
Source patient with terminal AIDS	5.6	2.0–16

Source: reference [5].

also extrapolated from the effect of antiretrovirals on perinatal transmission. A retrospective cohort study of 939 infants demonstrated that postnatal zidovudine prophylaxis within 48 hours of birth reduces the incidence of HIV transmission from 26.6% to 9.3%, even in the absence of maternal therapy [7]. The importance of the timing of PEP is supported by primate studies showing that PEP confers no benefit if initiated more than 24 hours postexposure [8,9].

The Cochrane review identified no studies that evaluated the effect of combination antiretroviral therapy for PEP following occupational exposure [6]. Reasons for considering combination therapy in this setting include enhanced treatment effectiveness for HIV-infected patients, enhanced effectiveness in preventing perinatal transmission, reduced risk of emergence of resistant strains, and potential exposure to zidovudine-resistant strains. Adverse effects are reported in over 70% of HCWs started on PEP [10,11]. The Cochrane review found that adverse events were significantly higher with the use of multi-drug regimens, but that discontinuation rates were not significantly different [6]. The Centers for Disease Control and Prevention (CDC) guidelines recommend a basic 4-week regimen of two drugs for most HIV exposures, and an expanded regimen that includes a third drug (usually a protease inhibitor) for HIV exposures that pose an increased risk for transmission (Table 18.1) [12,13].

Rapid HIV testing of the source following occupational exposure can significantly reduce the unnecessary use of PEP, the cost of managing HCWs receiving PEP and its associated side effects, and psychological stress [14,15]. When the source is unknown or cannot be tested, HCWs should be counseled to exercise sexual abstinence or use condoms [16], and not to donate blood, semen, or organs for the first 6–12 weeks following exposure.

Hepatitis B virus infection

Healthcare workers are at risk of occupational exposure to hepatitis B virus (HBV). Unvaccinated HCWs exposed to a source patient that is hepatitis B surface antigen (HBsAg)-positive and HBeAg-positive have a 22–31% risk of developing clinical hepatitis and a 37–62% risk of seroconversion. Unvaccinated healthcare workers exposed to a source patient that is HBsAg-positive, HBeAg-negative have a 1–6% of developing clinical hepatitis and a 23–37% risk of seroconversion [17].

Effective vaccines are now available to prevent occupational acquisition of HBV, and evidence from a Cochrane review supports occupational health guidelines that all HCWs should be offered HBV vaccination [18]. Since the availability of vaccines, the proportion of acute HBV cases in the United States related to occupational exposure has dropped from 4.5% to 0.5% [19].

Studies reported in the early 1980s showed an overall benefit of plasma-derived HBV vaccine for preventing HBV infection in HCWs (RR 0.51, 95% CI 0.35–0.73), although the differences were not significant for the low-risk HCWs (RR 0.20, 95% CI 0.02–1.70). Recombinant DNA HBV vaccines have been shown to be as safe and immunogenic as the original plasma-derived vaccine [18,20]. Attempts at administering reduced doses of vaccine intradermally have been unsuccessful. Six trials comparing full-dose intramuscular administration of plasma-derived or recombinant DNA HBV vaccine to low-dose intradermal administration have all demonstrated reduced incidence of protective immunity from intradermal administration [18].

There is no evidence that booster doses are necessary to maintain seropositive HBsAb titers [21]. Although not prospectively evaluated, most guidelines recommend serologic testing for hepatitis antibody after a primary immunization course has been completed. Approximately 10% of HCWs may fail to respond to HBV immunization (nonresponders). In one HCW study, factors associated with failure to develop protective levels of HBV antibodies included increasing age, obesity, smoking, and male gender [20]. Persons who do not respond to an initial three-dose vaccine series have a 30–50% chance of responding to a second three-dose series [12,22].

Postexposure vaccination of susceptible HCWs has been shown to be protective against the development of clinical hepatitis [23]. Hepatitis B immune globulin (HBIG) is also effective in preventing clinical infection postexposure [24]; however, HCWs who received HBIG were as likely as those who received immune serum globulin to develop subclinical infection [25]. The effectiveness of combined vaccination and HBIG following exposure has not been evaluated in the occupational setting; however, increased

efficacy of this combination compared with HBIG alone in preventing perinatal transmission provides indirect support of this practice [26]. Thus, unvaccinated (or incompletely vaccinated) HCWs should receive a single HBIG dose plus HBV vaccine following a significant exposure [12,27]. For HCWs who remain nonresponders after the second three-dose vaccination series, two doses of HBIG are recommended following a significant exposure [12].

Hepatitis C virus infection

Hepatitis C virus (HCV) is not efficiently transmitted by occupational exposure. The average transmission rate to more than 11 000 exposed HCWs from six countries was 0.5% (95% CI 0.39–0.65) [28]. Transmission occurred through percutaneous or mucosal exposure; no occupational transmission has been documented from intact or nonintact skin exposures [12].

There is no evidence of benefit of postexposure immunoglobulin prophylaxis for HCV and its use is not recommended [12,27]. Similarly, there have been no clinical trials evaluating the efficacy of antiviral agents (e.g., interferon or ribavirin) to prevent HCV infection following occupational exposure, and antivirals are not FDA-approved for this indication [12].

Early therapy of acute HCV has been studied, but heterogeneity of definitions of acute HCV disease and in the antiviral regimens used has made it difficult to interpret the results of these studies. In an open-label study which included 14 HCWs a 24-week course of interferon-α-2b prevented chronic HCV infection in 98% of patients and treatment was well tolerated [29].

A series of related intervention studies by Kamal and colleagues demonstrated no difference between peginterferon-α-2a compared to peginterferon-α-2b, a nonsignificant advantage to the addition of ribavirin, advantage to a longer (i.e., 24-week) course of therapy for genotype 1 virus (whereas 8-week or 12-week regimens sufficed for other genotypes), and an advantage to earlier initiation of therapy (i.e., 8 or 12 weeks after first evidence of biochemical hepatitis with positive HCV viremia demonstrated by PCR) [30–32]. Although uncertainty remains around the optimal antiviral regimen and duration of therapy, these studies demonstrate the importance of early diagnosis and treatment in the prevention of chronic HCV infection.

Current CDC guidelines recommend measuring HCV antibody at 4–6 months to detect infection [12], while European guidelines recommend testing for HCV antibody at baseline, 6 months, and 12 months, as well as alanine aminotransferase monthly for the first 4 months, with HCV PCR performed upon detection of abnormal results [27]. Current guidelines do not establish an optimal approach for treating HCWs occupationally infected with HCV, but it seems reasonable to undertake surveillance for biochemical hepatitis and seroconversion, confirm this with quantitative HCV PCR and genotyping, and then observe 8 to 12 weeks for spontaneous viral clearance before offering therapy for acute HCV with pegylated interferon, with or without ribavirin [33].

Prevention

Risk factors for bloodborne pathogen exposure include less-experienced or less-educated HCWs, HCWs in higher-workload centers, HCW fatigue, and extended duration of workshifts [34–36]. There have been few randomized trials evaluating the effectiveness of interventions to reduce exposures among HCWs. In one systematic review that included 11 randomized trials mostly focusing on surgical procedures, a reduction in sharps injuries and glove perforations was associated with double gloving, use of specialized needles for wound closure, use of safety-engineered devices, and use of a "no-touch" technique during wound closure [37].

A systematic review of 17 intervention studies of needleless or safety-engineered sharps systems demonstrated reduced incidence of percutaneous injury by 22–100% compared to pre-intervention, although involvement of HCWs in the selection and implementation of safety systems was important in the success of harm reduction strategies [38]. Several of these studies also demonstrated cost savings with implementation of safety-engineered devices.

Summary

Harm prevention strategies should incorporate education about safer work practices, particularly for more inexperienced healthcare workers, and incorporate "no-touch" surgical closure techniques and safety-engineered devices. Should a bloodborne pathogen exposure occur, HCW require prompt evaluation and management. For high-risk exposures,

combination antiretroviral therapy should be initiated promptly and rapid testing performed on the source patient. There is good evidence to support universal HBV vaccination of HCWs, but weak evidence for postexposure use of HBIG. Occupational exposures to HCV should be managed by surveillance for, and early treatment of, acute disease.

Case presentation 2

At the end of his 24-hour on-call shift, a resident asks his attending staff to look at his rash. It is obviously chickenpox. Infection Control and Occupational Health Services are promptly called for advice regarding management of the resident and his contacts. The resident believed he had chickenpox as a child, but had not been tested further. As a result of exposure to this resident, 15 healthcare workers spent 14 days of paid leave off work and 8 exposed patients were kept in respiratory isolation during the period they were potentially infectious. A recommendation is made for a thorough review of the screening protocols for healthcare workers and policies for vaccine-preventable infections.

Varicella zoster virus infections

Varicella zoster virus (VZV) causes chickenpox or varicella zoster. Although chickenpox is usually self-limited in children, it is generally more severe in adults and immunocompromised persons, with higher rates of pneumonia, encephalitis, and death reported [39]. Individuals at higher risk of complications include pregnant women, premature infants born to varicella susceptible mothers, infants born at less than 28 weeks gestation or weighing $\leqslant$1000 g (regardless of maternal immune status) and immunocompromised individuals [40]. The risk of congenital varicella syndrome following maternal infection during the first trimester of pregnancy has been estimated to be 2.2% (95% CI 0–4.6%) [41]. Following primary chickenpox infection, the virus remains dormant in sensory nerve ganglia and may reactivate, resulting in varicella zoster or shingles.

Nosocomial transmission of VZV is well recognized [39,42], and prevention and control measures are costly [43,44]. Thus, control measures in healthcare facilities are strongly recommended [42,45,46]. VZV is transmitted from person to person via direct contact with infected lesions, or airborne spread from either the lesions or respiratory tract secretions [39]. It is generally accepted that patients with localized zoster are less contagious than those with primary chickenpox or disseminated zoster; however, patients with localized zoster have been shown to be the source for extensive environmental contamination and aerosolization [47–49].

Although there have been no controlled clinical trials of the effectiveness of VZV vaccine in HCWs, a long-term prospective follow-up study of vaccinated HCWs showed that the attack rate following household and hospital exposure was reduced from an estimated 90% to 18% and 8% respectively, that all illness was mild to moderate (mean 40 vesicles), and that 96% of HCWs developed antibodies to varicella [50]. Based on these data, current guidelines recommend that all susceptible HCWs be immunized with two doses of standard-dose live attenuated VZV vaccine [39,42,46].

Most adults are immune to VZV because of infection during childhood. The sensitivity of a history of chickenpox for predicting serologic immunity in HCWs ranges from 79% to 100% [51–55], with a high positive predictive value (98–100%) but a negative predictive value of less than 10%. Thus, HCWs who give a history of chickenpox as a child may be considered to be immune [56]. However, those with an uncertain or negative history of chickenpox should have a serologic test to determine susceptibility [39,42,46]. Overall, less than 5% of HCWs in the western world lack serologic immunity to VZV [52–54]; however, HCWs from Africa, the Middle East, and East Asia may be at higher risk (12–19% lack seroprotection) [57]. Serologic testing of all staff with a negative or uncertain history of VZV, and vaccinating those who are seronegative, was found to be a cost-effective strategy by both modeling and clinical studies [58–60]. Post-vaccination serologic testing is not recommended, as 94–99% of adults will develop immunity [61,62].

It is recommended that susceptible HCWs (i.e., seronegative HCWs who have not been vaccinated) be excluded from work from days 8 to 21 following a significant exposure [39,40,42,45,46]. However, there

is variation between current guidelines as to what constitutes a significant varicella exposure [39,46,63]. Proposed postexposure strategies for managing these susceptible HCWs have included vaccination, varicella-zoster immune globulin (VZIG), and antivirals. Controlled studies of postexposure prophylaxis using VZV vaccine in HCWs have not been carried out. A review of current evidence suggests that postexposure vaccination of children within 3 days of rash onset of the index case appears to be an effective preventive measure [63]. For the small proportion of contacts that develop infectious VZV despite vaccination, the clinical illness is mild. These data have been extrapolated to support recommendations for postexposure vaccination in healthcare settings, however, pre-employment testing and vaccination remains the preferred approach [39,42,46].

There is no evidence to support the routine use of VZIG in healthy HCWs exposed to chickenpox. VZIG administered within 96 hours after exposure has been shown in observational studies to prevent or modify clinical illness in nonimmune, immunocompromised persons who are exposed to varicella [64–66]. An observational study in neonates found that VZIG reduced the incidence of varicella disease if the mother had chickenpox during the last week of pregnancy [67]. Based on these observational studies, VZIG is recommended postexposure for immunocompromised or pregnant HCWs who are susceptible [39,46]; however, there is no evidence from controlled trials to support this approach. It should be noted that VZIG may extend the incubation period of the virus from 10–21 days to $\geqslant$28 days, and this should be taken into account when excluding susceptible, exposed HCWs from work.

There are few studies evaluating the use of acyclovir as postexposure prophylaxis. In one report two varicella-susceptible resident physicians were deliberately exposed to an infected child and then given a 7-day course of acyclovir beginning 9 to 11 days postexposure. Both residents developed limited disease (less than 48 hours' duration, fewer than five lesions) and developed protective immunity by the fourth week postexposure [68]. In two small household studies, 7.4% and 16% of contacts given acyclovir developed disease compared with 77% and 100% of contacts who were not given acyclovir [69,70]; however, acyclovir use was associated with a decreased rate of seroconversion and approximately half of the contacts remained susceptible to VZV [45]. VZV infection following prophylactic acyclovir use has been reported [71]. Based on current evidence, the prophylactic use of acyclovir is not recommended; postexposure vaccination remains the approach of choice for otherwise healthy susceptible individuals and VZIG is recommended for immunocompromised individuals [39,46].

Summary

Nosocomial transmission of varicella to susceptible HCWs is a risk both to the health of the worker as well as their patients. The key prevention strategy is pre-employment screening of HCWs, and providing vaccination to those susceptible. Postexposure vaccination of susceptible HCWs within 3 days of exposure is a secondary prevention measure. The indications for prophylactic VZIG are very limited, and prophylactic acyclovir is not recommended.

Case presentation 3

You are approached by an emergency department nurse concerned about a patient she treated during her last shift. The patient is an elderly woman who presented with fever, cough, and shortness of breath. The nurse tended to this patient in an open stretcher bay for some time prior to the initial physician assessment, and afterwards was dismayed to learn that the patient had presumed influenza. The nurse, like many of her colleagues, declined influenza vaccine this year citing concern regarding possible adverse reactions, and is now worried about becoming ill. She wants to know what steps can be taken to ameliorate her risk now, and for future exposures.

Influenza-like illness

Influenza

Influenza epidemics and pandemics have had a remarkable societal impact throughout history. One review of the socioeconomic burden of influenza suggests that the indirect costs associated with annual influenza epidemics (including work absenteeism and loss of productivity) are up to 10-fold higher than the

direct costs of medical care [72]. Nosocomial influenza is one of the most common pathogens resulting in closure of clinical units, generating additional healthcare costs and impacting patient care [73]. Elderly or chronically ill adults are at increased risk for pneumonia, hospitalization, and death related to influenza; however, healthy HCWs become part of the chain of transmission of influenza during outbreaks, particularly in nosocomial transmission [74].

A Cochrane review assessing the effectiveness of the influenza vaccine demonstrated a 62% reduction in laboratory-confirmed cases of influenza in healthy adults (95% CI 45–73%) for the live aerosol vaccine and an 80% reduction (95% CI 56–91%) for the inactivated parenteral vaccine, but only a modest effect on non-laboratory-confirmed disease ("influenza-like illness", ILI) of 10% and 30% respectively [75]. Vaccination was also associated with a significant reduction in work absenteeism. A recent review of three randomized controlled trials of HCW influenza vaccination revealed conflicting results [76], with one study showing a significant reduction in serologically confirmed influenza of 88% (95% CI 47–97%) but no significant reduction in work absenteeism [77], one study showing no difference in ILI but a significant reduction in work absenteeism due to ILI [78], and the third study showing no significant difference in rates of ILI or work absenteeism [79]. The lack of effect in the third study was explained by a poor match between the vaccine strains and the circulating strains. Vaccination was safe and well-tolerated in all three studies [76].

Another recent Cochrane review found that HCW vaccination significantly reduces ILI in patients (but only when patients are vaccinated too), death from pneumonia, and death from all causes [80]. There was no effect on confirmed influenza cases or lower respiratory tract infection; however, systematic laboratory testing of patients to confirm an influenza diagnosis was not done. An economic evaluation using UK data suggests that HCW vaccination saves approximately £12 in healthcare costs per vaccine administered based on reduced work absenteeism [76]. Thus, several national guidelines strongly recommend annual influenza vaccine for patients and HCWs as a means of preventing transmission in healthcare facilities [42,46].

The uptake of influenza vaccine amongst HCWs varies widely between studies, from as low as 2% [76] to as high as 82% [81]. Two recent reviews found that the major barriers to vaccination were: (1) HCWs' misperception of the need for vaccination; (2) lack of (or perceived lack of) conveniently available vaccine; (3) misperception of vaccine effectiveness; (4) fear of adverse effects; (5) fear that the vaccine would cause influenza; and (6) fear of injections or needles [76,81]. A review of seven controlled studies evaluating the effect of promotional campaigns on HCW influenza vaccination rates yielded variable results, and found that studies performed to date are limited by bias, confounding, incomplete reporting, and lack of long-term follow-up [76]. These studies reported baseline vaccination rates of 5–17% with increases of 5–45% in response to vaccination campaigns. The best-designed study in this review, a cluster-randomized controlled trial, showed no increase in vaccination uptake by HCWs despite an intensive promotional campaign [82]. Thus, uncertainty remains around whether behavioral interventions can improve HCW influenza vaccination coverage in a sustained manner. As a result, some consideration had been given to making influenza vaccination mandatory [83]. In the meantime, for HCWs concerned about side effects, there is good evidence from a placebo-controlled trial that acetaminophen will significantly reduce symptoms of sore arm and nausea associated with the vaccine [84].

There are no controlled trials assessing the effect of antiviral prophylaxis in HCWs [85]. A Cochrane systematic review showed that neuraminidase inhibitor prophylaxis in adults was not effective in preventing ILI, although it did prevent laboratory-confirmed influenza (dose- and agent-dependent: oseltamivir 150 mg per day most efficacious at 73%) [85]. Another Cochrane review showed that amantadine prevented 25% of cases of ILI (95% CI 13–36%) and 61% of laboratory-confirmed influenza A, but was associated with significant gastrointestinal side effects [86]. Based on these findings, current guidelines recommend antiviral prophylaxis for the management of unimmunized HCWs during a nosocomial outbreak; however, vaccination remains the preferred preventive measure [87].

Institutional measures to control ILI – the SARS experience

The role of HCWs in both nosocomial and community-based transmission of ILI was dramatically highlighted during the 2003 severe acute respiratory syndrome (SARS) outbreak [88–90]. Worldwide,

HCWs composed approximately 5% of all SARS cases; however, in some countries (including Vietnam, Singapore, and Canada) HCWs represented over 40% of all cases [90]. In these countries, several factors were associated with transmission of SARS to and from HCWs, and these factors are likely to apply to transmission of other etiologies of ILI. These include HCWs working while ill ("presenteeism"), inadequate use of personal protective equipment (such as gloves, gowns, masks), poor hand hygiene practices, and most fundamentally, a lack of early recognition of the severity and transmissibility of the illness [88,89,91]. Thus, recent guidelines on respiratory hygiene recommend that appropriate precautions (e.g., masking and/or isolating patients) be initiated for all patients ill with ILI at the initial point of healthcare contact (e.g., upon registration or triage), rather than being delayed until after medical assessment [92].

Prevention of other infections in healthcare workers

General measures

Many issues noted in the transmission of SARS to and from HCWs stem from inappropriate attention to previous infection control/occupational health standards, and likely apply to other occupational exposures as well. For example, a case–control analysis of SARS exposure among HCWs in Singapore demonstrated a protective relationship between post-patient contact handwashing and incidence of SARS (OR 0.07; 95% CI 0.008–0.66) [89].

There is evidence among other populations that hand hygiene is a self-protective measure. A cluster-randomized trial among university students noted that a hand hygiene campaign decreased incidence of ILI 20%, with a 43% reduction in absentee days [93]. Similarly, a cluster-randomized study of a hand hygiene campaign among military personnel noted a 40% reduction in outpatient visits for ILI, a 48% reduction in diarrheal illness, and a 44% reduction in lost training time due to illness [94]. A Cochrane systematic review supports the use of handwashing to reduce diarrheal illness in institutional and community settings [95]. Unfortunately HCW compliance with hand hygiene standards is often suboptimal [96], as is compliance with other infection control/occupational health recommendations such as use of personal protective equipment [97], and avoidance of "presenteeism" (presenting to work while ill) [98].

Other infections

Nosocomial transmission of measles and rubella is well documented [99]. A number of observational studies have shown that serologic screening of HCWs before immunization is cost-effective for measles [100–102]. A history of disease or vaccination can be unreliable [103]. Immunization of HCWs who do not have evidence of immunity against measles, mumps, and rubella is strongly recommended [42,46], with evidence from case–control and cohort studies supporting a vaccine efficacy of greater than 95% [104–106].

Invasive meningococcal disease is associated with a case fatality rate of up to 10%. There are no controlled trials on the effects of prophylactic antibiotics on the incidence of meningococcal disease nor good evidence to identify which contacts should be treated [107]. Although there are reports of transmission of infection to HCWs, nosocomial transmission is extremely rare. In a retrospective survey from England and Wales the risk of invasive meningococcal disease in HCWs was 0.8 per 100 000 HCWs exposed to meningococcal disease, roughly 25 times that in the general population; however, the authors of the study concluded that the excess risk was small [108]. Nonetheless, based on case reports of meningococcal infection in HCWs with unprotected airway exposure to respiratory droplets from patients with meningococcal infection, occupational health guidelines recommend prophylaxis in these settings [42]. There is evidence from randomized trials, using eradication of *Neisseria meningitidis* as the endpoint, to support the use of rifampin, single-dose ceftriaxone, or single-dose ciprofloxacin for PEP [109–110].

Using retrospective data on cases of laboratory-acquired invasive meningococcal disease, the CDC estimated an increased attack rate of 13 per 100 000 population (95% CI 5–29) and recommended that vaccination be considered for laboratory workers working with isolates of *Neisseria meningitidis* [111]. The vaccine, however, will only protect against meningococcal disease caused by serogroups contained in the vaccine.

Summary

There is good evidence, in many instances from controlled trials, to support current guidelines for

the screening and immunization of HCWs against vaccine-preventable infections. Infection control standards should be reinforced among HCWs, and control measures put in place early in the care of potentially infectious patients.

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CHAPTER 19

Infections in long-term care

Lindsay E. Nicolle

Case presentation

The nursing staff at a long-term care facility contact you to assess a resident who the ward staff are concerned is "not well." This woman is 85 years old, and requires permanent institutional care because of progressive Alzheimer disease. She is incontinent of urine, but controlled with a toileting program, and is a "wanderer." There is no history from the patient. The nursing staff say she has not been as active as usual, and has been eating poorly for the past several days. The patient has a past history of complete heart block for which a pacemaker was inserted, and congestive heart failure. Her temperature is 37.9°C, respiratory rate 24, pulse a paced rate of 72, and blood pressure 120/80. The physical examination reveals no abnormalities of the skin, bilateral inspiratory crepitations in both lung fields, a mildly elevated JVP, and bilateral pedal edema. The nursing staff say they obtained a urine specimen as the urine was "foul smelling," and a dipstick is positive for leukocyte esterase. They request you to order antimicrobial therapy for urinary infection.

As you are already at the facility, you are requested to assess a second resident. This is a 92-year-old male with obstruction secondary to prostate hypertrophy managed with a chronic indwelling catheter. He is aphasic and hemiplegic following a stroke. The nursing staff notes that his temperature is 38.2°C, and he is "restless." Physical examination reveals poor inspiration bilaterally but no adventitial signs. There are no skin lesions. The nursing staff have also obtained a urine specimen from his Foley drainage bag and this, too, is leukocyte esterase positive. Again, they request an order for antimicrobial therapy.

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Long-term care facilities

Long-term care facilities provide long-term residential care for individuals who are unable to function independently. A variety of different facilities serve diverse patient populations including pediatric and adult, psychiatric, and patients requiring long-term interventions such as chronic respirator therapy or chronic hemodialysis. The majority of long-term care facilities, however, provide permanent residential care for elderly, functionally impaired adults. Information characterizing infections in long-term care facilities is primarily relevant to these facilities and residents, and this is the population addressed in this chapter.

The goals of care for long-term care facilities differ from acute care. The long-term care facility is the permanent residence for most of these individuals. The major goal is to maximize quality of life for residents. This includes maintaining optimal medical status, functional capacity, and social activity while preserving resident comfort and dignity. These facilities also differ fundamentally from the acute care facility in being a low-technology environment. The intensity of care and access to both expertise and technology which characterize the acute care facility are not available nor appropriate for long-term care. Patient management and institutional practices should not be imported from acute to long-term care facilities without evidence of benefit for the long-term care facility resident.

Infections in long-term care facilities

Incidence of infections

Infections are common in residents of long-term care facilities [1]. The most frequent endemic infections are lower respiratory tract infections – primarily

Table 19.1 Reported rates of common endemic infections in long-term care facilities

	Rate per 1000 resident days				
Location [reference]	**Multiple studies [1]**	**Idaho, USA [2]**	**Germany [3]**	**Italy [4]**	**Norway [5]**
All infections	2.6–9.5	3.73 (1.45–6.96)*	6.0	11.8	5.2
Respiratory	0.46–4.4	1.75 (0.79–2.85)	2.2	2.5	1.4
Urinary	0.1–2.4	0.57 (0–2.28	1.2	3.2	2.0
Skin/soft tissue	<0.1–2.1	1.19 (0.66–2.67)	1.0	2.7	0.5
Gastroenteritis	0–0.9	0.16 (0–0.64)	1.2	1.2	0.4

Source: references [1–5].
* Mean (range) for multiple facilities.

pneumonia – skin and soft-tissue infections, symptomatic urinary tract infections, and gastrointestinal infections (Table 19.1). The incidence and relative frequency of infections have been consistent in reports from developed countries over several decades [1–5]. Wide variations in endemic infection rates, particularly for urinary tract infection or pneumonia, are reported among some studies [1]. This variability is partially attributable to the different patient populations described. For instance, bacteremia rates are higher in facilities providing care for chronic hemodialysis patients with indwelling vascular lines, and the incidence of pneumonia is higher in facilities caring for residents with chronic tracheostomies. Infection rates are lower in psychiatric facilities which care for younger individuals with few comorbidities. Thus, infection rates must be interpreted within the context of the facility population. The reported variation in infection rates is also partially attributable to the use of different definitions for case ascertainment [6]. This is particularly an issue for urinary tract infection, where symptomatic and asymptomatic infection may be confused. A recent report of infections in Idaho, USA, nursing homes using a standard surveillance strategy for definitions and case-finding together with consistent training of data abstractors reported a narrower range of infection rates among facilities, although some interfacility variation remained [2].

Outbreaks of infections also occur frequently in long-term care facilities. The microbial etiology of these outbreaks is wide, and new organisms are continually being implicated (Table 19.2). Respiratory and gastroenteritis outbreaks are most frequent. Influenza viruses [7] and noroviruses [8] are the most common organisms and have the greatest impact. Scabies and, occasionally, group A streptococcal infection [9] are less common but may cause problematic outbreaks of skin infections.

Factors promoting infection

Many variables contribute to the high incidence of infection in long-term care facility residents. Normal aging changes in organ systems, including the immune system, may promote infection (Table 19.3). A decline in cell-mediated immunity is a consistent accompaniment of aging and contributes to increased rates of reactivation of latent infections such as tuberculosis [10] and varicella zoster virus [11]. Other aging-associated alterations in the immune system have not been associated with infections in long-term care residents. It is likely changes associated with normal aging in other body systems increase the risk of infection, but the relative importance of these compared with other contributing factors is not known.

The most important factors promoting infection are associated chronic diseases and functional disability. These are also the most frequent causes precipitating the need for institutional care. The more functionally impaired elderly – those who are immobile, incontinent, and unable to provide self-care – are at greatest risk of infection [12]. For instance, aspiration is an important precipitating event for pneumonia, and swallowing impairment following a stroke increases the risk of aspiration. Voiding abnormalities accompanying chronic neurologic diseases lead to both incontinence and an increased likelihood of urinary tract infection. Peripheral vascular disease and leg edema both contribute to leg and foot ulcerations and infection. Previous leg vein stripping for coronary artery bypass surgery is a risk for recurrent erysipelas,

Table 19.2 Organisms identified as causes of outbreaks of infection in long-term care facilities

	Viral	Bacterial	Other
Respiratory outbreaks	Influenza A & B* Respiratory syncytial virus* Human metapneumovirus Parainfluenza Coronavirus Adenovirus Rhinovirus	*Mycobacterium tuberculosis* *Streptococcus pneumoniae* *Chlamydia pneumoniae* *Hemophilus influenzae* *Legionella* spp *Bordatella pertussis*	
Gastrointestinal	Norovirus* Astrovirus Hepatitis B Rotavirus	*Salmonella* spp* *Shigella* spp *E. coli* O157:H7 *Clostridium difficile* Foodborne toxin (*S. aureus*, *Bacillus cereus*, *Clostridium perfringens*) *Campylobacter jejuni* *Aeromonas hydrophilia*	*Giardia lamblia* *Entamoeba histolytica*
Skin/soft-tissue infection		Group A streptococcus +	Fleas Scabies *Trychophyton* spp.
Resistant bacteria		Methicillin-resistant *S. aureus* Vancomycin-resistant enterococcus Penicillin-resistant *S. pneumoniae* TEM-21 producing *Pseudomonas aeruginosa*	

* Most common organisms causing outbreaks.
+ Also causes respiratory infections.

Table 19.3 Some organ system changes with normal aging which may promote infection

System	Aging change	Impact
Pulmonary	↓ cough reflex ↓ elastic tissue ↓ mucociliary transport ↓ IgA secretion	↓ clearing of secretions
Gastrointestinal	impaired oropharynx neuromuscular coordination altered gut motility ↓ mucosal immunity	↑ dysphagia, choking, aspiration ↑ infection
Genitourinary	↑ prostate size (men) hypoestrogenism (women)	obstruction, turbulent urine flow altered vaginal flora
Skin	epidermal thinning ↓ elasticity, vascularity, thermoregulation, melanocytes, Langerhans cells, subcutaneous tissue	↑ injury potential ↓ wound healing
Immune	↓T-cell function ↓ primary humoral response ↑ autoantibiotic ↑ Th_2 inflammatory response	↑reactivation latent infections

and immobility contributes to development of decubitus ulcers which may become infected.

Interventions for medical care also promote infection. Invasive devices are increasingly used for management of chronic illness in long-term care facility residents. Chronic indwelling urethral catheters are used to manage voiding for 3–7% of residents [13], and percutaneous feeding tubes, central vascular lines, and chronic tracheostomies are increasingly used for patient management. All invasive devices promote infections specific to the device – urinary infection with chronic indwelling catheters, ventilator-associated pneumonia for patients with chronic tracheostomies, bacteremia when central vascular lines are present, and insertion site infections when percutaneous feeding tubes are used. In addition, polypharmacy is the norm for residents of long-term care, and some common medications such as proton pump inhibitors are associated with an increased risk of infection [14].

Finally, institutionalization itself increases exposure to infectious agents. Staff members and visitors introduce pathogens into the facility. Transmission of infectious agents among residents is facilitated through repeated close interactions of staff and residents in the long-term care environment. It is not surprising that outbreaks occur in this vulnerable population with repeated exposures to pathogens and facilitated transmission of organisms within a closed environment.

Impact of infections

For the infected resident, the discomfort and activity restriction attending an episode of infection is associated with a decreased quality of life. Residents experience accelerated functional decline during the 6 months subsequent to an infection [12]. Whether this deterioration is attributable to infection or the infection is an association of accelerated decline is not known. Infections may also lead to serious complications, such as pneumonia precipitating a myocardial infarction or foot infection requiring amputation. There are adverse impacts for the institution as well including costs for investigation and treatment of the infected resident, and transfer to acute care facilities for care in some cases. Outbreaks of infection are associated with substantial additional costs for treatment and control. Considerable disruption to usual facility activities accompany outbreaks of infection, and all residents are negatively affected irrespective of whether they are themselves infected.

Despite the high frequency of infection, only pneumonia and influenza contribute substantially to resident mortality. Between 6% and 23% of residents who develop lower respiratory infection will die [15], and case fatality rates in influenza outbreaks, even with effective vaccination programs, range from 5% to 55% [6]. Gastrointestinal outbreaks of salmonella infection [14] or *E. coli* O157:H7, and skin and respiratory outbreaks of group A streptococcal infection [16], are much less common, but when they occur may also be associated with high case-fatality rates.

Diagnosis

General clinical considerations

Infection in a long-term care facility resident may have a clinical presentation similar to younger populations. However, in many cases the diagnosis is not straightforward. Determining whether or not infection is present, or the specific site when infection is suspected, is frequently problematic [17,18]. Clinical assessment is compromised by limited communication when residents have impaired hearing or vision, or decreased mental capacity. Chronic symptoms accompanying comorbid illnesses, such as cough, dyspnea, or venous insufficiency, compromise the interpretation of acute signs and symptoms of infection. Infection may also present with nonspecific findings such as lethargy, decreased appetite, or increased functional impairment [17,19]. Acute delirium is a common presentation of severe infection in this population. These nonspecific signs and symptoms are, however, also frequently attributable to noninfectious problems such as dehydration, adverse drug effects, drug interactions, fecal impaction, or exacerbation of comorbid illness.

The temperature response in elderly individuals is attenuated relative to younger populations [17]. The maximum temperature achieved with infection is, on average, lower and elderly persons are more likely to experience afebrile infection. A temperature of $>37.8^{o}$C has been reported to provide optimal sensitivity and specificity for identifying infection in long-term care facility residents [20]. Some elderly residents have a relatively hypothermic baseline

temperature, and measured temperatures should be interpreted in the context of the individual's usual baseline. Notwithstanding these caveats, episodes of serious systemic infections will usually be accompanied by a documented fever. For instance, in a large series of bacteremias in nursing home residents, only 10% of episodes were afebrile [21].

Laboratory evaluation and diagnostic imaging

Long-term care facilities have restricted access to diagnostic investigations. Diagnostic facilities are usually offsite and clinical specimens must be transported to the laboratory [17,18,22]. The receipt of test results may be delayed. Mobile chest radiographs provide onsite diagnostic imaging for some facilities, but availability is usually restricted to daytime hours [18]. For other diagnostic imaging investigations, the resident must be transferred to another facility.

The peripheral leukocyte count should be interpreted in the context of patient age and disability. Elderly individuals with infections are less likely to demonstrate peripheral leukocytosis than younger patients [17,23]. Evidence of marrow stress is, however, usually evidenced by a left shift with increased bands on the leukocyte differential. A proportional band count of 15%, or an absolute number of $\geqslant$1500 bands/mL, correlates with infection in elderly individuals, even with a normal leukocyte count [23].

A critical interpretation of positive microbiology cultures is also essential. Colonization with potentially pathogenic organisms in the absence of infection is common in the oropharynx [1] and for open skin lesions [24,25], and there is a high prevalence of asymptomatic bacteriuria in urine specimens [26]. Cultures should be obtained only when there is a clear clinical indication, and results interpreted in the context of this high prevalence of colonization.

Blood cultures should be requested for elderly residents where a diagnosis of serious systemic infection is considered [17]. They must be collected before the initiation of antimicrobial therapy. The most common source of bacteremia is urinary infection [1,21], with a chronic indwelling catheter the major risk factor for bacteremia [27]. Infected decubitus ulcers and the respiratory tract are other common sources of bacteremia. Urinary infection and infected decubitus ulcers are the source for 70–80% of bacteremic episodes [21]. When polycrobial bacteremia is identified, an infected pressure ulcer is the most common origin.

Pneumonia

The most useful clinical indicator when a diagnosis of pneumonia is considered is a respiratory rate over 25 breaths per minute. This level of tachypnea had a sensitivity of 90% and specificity of 95% for pneumonia in one study [28]. Other clinical indicators helpful in diagnosing pneumonia include fever, a change in character or quantity of sputum, and increased cough. Oximetry may be a useful test for the diagnosis and evaluation of respiratory tract infection but is not yet accessible in many facilities and has not been critically evaluated for use in this population [17]. Even when a chest radiograph is obtained, the interpretation is not straightforward. Chronic changes, congestive heart failure, chemical pneumonitis, and other findings may be misattributed to pneumonia. There is low interobserver consistency among radiologists in the identification of pneumonia on chest radiographs from long-term care facility residents [29].

Guidelines of the Infectious Diseases Society of America (IDSA) [17] recommend, when a diagnosis of pneumonia is considered in a long-term care facility resident, a respiratory rate should be obtained. If the respiratory rate is $\geqslant$25, then pulse oximetry should be obtained, and if pulse oximetry is less than 90%, a chest radiograph should be requested. The utility of this suggested algorithm, or of individual components, has not yet been rigorously evaluated. Consensus guidelines for initiation of antimicrobial therapy in the long-term care facility recommend antimicrobial therapy should be initiated for presumed pneumonia when either: temperature is greater than 38.9°C and there is one of respiratory rate $>$25 breaths per minute or a productive cough; or temperature is greater than 37.9°C and there is new or increased cough with at least one of pulse $>$100 beats per minute, delirium, rigors, or a respiratory rate $>$25 breaths per minute [18]. One consideration in the differential diagnosis of pneumonia is chemical pneumonitis – a common problem in residents following aspiration of gastric contents. It has been proposed that pneumonitis can be differentiated from pneumonia in residents with a positive chest radiograph on the basis of history of

witnessed aspiration and duration of symptoms less than 24 hours [30].

The IDSA guidelines also recommend a sputum specimen for culture should be obtained if a diagnosis of pneumonia is made [17]. However, less than 5% of nursing home residents with suspected pneumonia will have a sputum specimen obtained [22]. This limited use of sputum specimens is partially attributable to difficulty in obtaining specimens from residents who are unable or unwilling to cooperate. Even when sputum specimens are obtained, interpretation of positive cultures is problematic because of contamination by gram-negative organisms colonizing the oropharynx, such as *Klebsiella pneumoniae* [1]. These organisms are isolated from the sputum specimen, but are seldom the etiology of infection. However, isolation of gram-negative organisms from sputum specimens drives broad-spectrum antimicrobial use, likely contributing to increased antimicrobial resistance. Sputum specimens may occasionally, however, be helpful in directing antimicrobial therapy, especially if *Streptococcus pneumoniae* is isolated. The collection of sputum specimens or nasopharyngeal aspirates for viral and bacterial culture is essential when there is a potential or confirmed outbreak of respiratory infection.

Thus, pneumonia is a potential diagnosis in the long-term care resident who is febrile and tachypneic. Alternate diagnoses, including congestive heart failure, infection at another site, pulmonary embolus, and pneumonitis should always be considered. The peripheral leukocyte count and differential, and oximetry if available, may be useful to assess the severity of the initial infection and monitor subsequent response to therapy.

Urinary infection

Symptomatic urinary tract infection is diagnosed in residents without indwelling urethral catheters when there are localizing genitourinary signs and symptoms [18,31,32]. Acute onset of symptoms such as frequency, dysuria, or new or increased incontinence support a diagnosis of urinary tract infection. Renal infection is usually accompanied by costovertebral angle pain or tenderness, although this may be difficult to appreciate in the most functionally impaired resident. Fever without localizing findings is unlikely to be from a urinary source in residents without an indwelling urethral catheter [32]. For residents with a chronic indwelling urethral catheter, however, the most common presentation of symptomatic urinary infection is fever without localizing findings [18]. Hematuria following catheter trauma and catheter obstruction are also both associated with invasive (i.e., febrile) urinary infection. Cloudy or foul-smelling urine are frequently interpreted as urinary infection in residents with or without chronic catheters. These signs may accompany bacteriuria or dehydration [29] but should not, by themselves, be interpreted as symptomatic infection or an indication for antimicrobial therapy [18,31].

A positive urine culture is useful to confirm the diagnosis of urinary infection and identify the specific infecting organism and susceptibilities. This is essential information to assist with appropriate antimicrobial selection. However, 30–50% of residents in long-term care facilities have positive urine cultures at any time [26]. Thus a positive urine culture in the absence of localizing genitourinary findings has a low positive predictive value for the diagnosis of symptomatic urinary infection [32]. Pyuria is a consistent accompaniment of bacteriuria in this population and is also not an indication for antimicrobial therapy in the absence of localizing symptoms [26]. However, a negative urine culture or the absence of pyuria both have high negative predictive values and are useful tests to exclude urinary tract infection [17].

The urine specimen should always be obtained before antimicrobial therapy is initiated, using a collection method which limits contamination. For men, a clean-catch urine specimen can usually be collected, or a specimen obtained from a freshly applied clean condom catheter and leg bag. For incontinent or uncooperative female residents, when a urine specimen is essential for management, in and out catheterization may be necessary. Residents with chronic indwelling catheters uniformly have positive urine cultures. Chronic indwelling urinary catheters are consistently coated with a bacterial biofilm which incorporates three to five different organisms. When symptomatic urinary infection is a diagnostic consideration, the indwelling urethral catheter should be removed and replaced by a new catheter [33]. The urine specimen for culture should be obtained through the new catheter, as this is a sample of

bladder urine rather than organisms in the biofilm. Obviously, catheter replacement and specimen collection should occur before antimicrobials are initiated.

Skin infections

The clinical diagnosis of erysipelas – spreading erythema, swelling, and tenderness with a well-demarcated border, usually affecting the face, arm, or leg – is often straightforward. However, acute erythema of the lower leg may occur with venous insufficiency or edema, and these presentations may be misdiagnosed as skin infection. The presence of a pressure ulcer or leg or foot ulcer is clinically apparent. The diagnosis of infection of a chronic ulcer requires the presence of signs such as induration, tenderness, erythema at the margins, or purulent drainage [18].

For clinical presentations consistent with erysipelas, especially in residents with recurrent episodes at the same site, β-hemolytic streptococci are the presumed pathogens, and a specimen for culture is not normally recommended. If purulent drainage is present, a specimen should be obtained for culture prior to initiating antimicrobial therapy. Organisms isolated from a surface swab of mucosa or open skin lesions, however, should not be interpreted as infection without associated signs and symptoms consistent with infection. A culture from a potentially infected ulcer should be obtained after the ulcer is debrided, so a deep swab sampling the base of the ulcer is obtained [25]. When there is necrosis present both aerobic and anaerobic cultures should be requested. Subcutaneous aspiration from the margin of a decubitus ulcer has been suggested as a means to differentiate infection from colonization, with growth from the aspirate presumed evidence for tissue invasion. However, this approach for specimen collection has not been validated, and noninfected ulcers may also have organisms isolated from aspirates [25].

Other skin infections such as varicella zoster (shingles), herpes virus, intertriginous candidiasis, and tinea are usually diagnosed by characteristic clinical presentations. The diagnosis of scabies is sometimes problematic. Prolonged outbreaks of scabies following delayed diagnosis of initial cases in long-term facility residents are repeatedly reported [34,35]. Scrapings to identify the mite are recommended, but may be negative in cases which are subsequently confirmed. A high index of suspicion is necessary, with dermatologic consultation and biopsy requested when the diagnosis remains uncertain.

Treatment

Antimicrobial use in long-term care

There is intense antimicrobial use in long-term care facilities. Between 22% and 89% of antimicrobial use has been reported to be inappropriate [18], although inappropriate use is a consistent problem in all healthcare settings [36]. Inappropriate use includes treatment of residents presenting with nonspecific symptoms or positive culture results without signs or symptoms to support a diagnosis of infection, or prescription of an antimicrobial regimen inappropriate for the site of infection or infecting organism. Antimicrobial prescriptions are often initiated at the request of nursing staff, without direct physician evaluation of the patient [17]. The limited access to diagnostic tests and complexity in clinical interpretation contribute to overuse of empiric antimicrobial therapy. Broad-spectrum antimicrobial use is frequently initiated because of uncertainty about the diagnosis or concerns about antimicrobial-resistant organisms.

Non-antimicrobial approaches

Potential noninfectious causes should always be considered when residents present with nonspecific signs and symptoms. These nonspecific clinical alterations are unlikely to be attributable to serious infection in the absence of fever [19]. Deterioration of congestive heart failure may explain cough, dyspnea, and tachypnea, and lethargy may be secondary to medication use. "Foul-smelling urine" will frequently respond to rehydration, while fever may be a sign of fecal impaction. Pneumonia must be differentiated from aspiration pneumonitis, which will resolve without antimicrobial therapy [30]. Thus, thoughtful, critical, clinical evaluation is essential for optimal management.

Episodes of fever in long-term care facility residents will often resolve without antimicrobial therapy [37]. When the diagnosis of infection is not definitive and clinical symptoms are of mild or moderate severity, a reasonable approach is to address potential contributing factors such as dehydration or constipation

and monitor the clinical status, rather than initiating empiric antimicrobial therapy [18]. This approach, however, has not yet been evaluated in prospective clinical trials. In addition, physicians or nurse practitioners may not be available to provide continuing clinical reassessment, and this may compromise a "wait and see" approach to management [17].

Initiation of antimicrobial therapy

Even with optimal clinical evaluation and monitoring, the decision to initiate antimicrobial therapy is often not clear-cut. Consensus guidelines proposing minimum criteria for initiation of antimicrobial therapy for presumed infections have been developed to address this uncertainty [18]. These proposed guidelines are based on clinical presentation rather than diagnostic tests, so are relevant to the diagnostic uncertainty which often accompanies long-term care facility residents with potential infection.

The utility of these guidelines for urinary infection have been evaluated from the perspective of limiting antimicrobial treatment of asymptomatic bacteriuria [38]. In a randomized, controlled trial, implementation of a multifaceted approach to antimicrobial treatment of urinary infection, including diagnostic and treatment algorithms, together with an intense educational strategy (small-group interactive sessions for nurses, videotapes, written material, outreach visits, and one-on-one interviews with physicians) was associated with a significant decrease in antimicrobials prescribed for suspected urinary infection when compared to usual care homes. However, total antimicrobial use for all indications did not differ between the intervention and usual care homes. This suggests there was a shift of diagnoses for residents with nonlocalizing presentations, with justification for empiric antimicrobial use based on diagnoses other than urinary infection. This study highlights the complexity of addressing the issue of optimal antimicrobial use in long-term care facilities.

The consensus guideline recommendations for initiating antimicrobial therapy for treatment of pneumonia and other lower respiratory tract infections have also been evaluated as a component of a clinical pathway in a study which randomized long-term care facility residents with pneumonia to management in the long-term care facility or transfer to an acute care facility. Management in the facility was associated with significantly reduced hospitalizations and healthcare costs, and comparable clinical outcomes [39]. A study comparing aspiration pneumonitis with pneumonia reported that presenting symptoms and signs, laboratory tests, severity of illness, or C-reactive protein levels did not distinguish between pneumonia and pneumonitis [30]. The authors propose an algorithm to differentiate these clinical presentations which includes witnessed aspiration of gastric contents, positive chest radiograph, and symptoms $<$24 hours from the aspiration event. This algorithm requires further evaluation to determine the utility for identifying pneumonitis and, possibly, limiting unnecessary antimicrobial exposure.

For urinary tract infection, antimicrobial therapy should, if possible, be delayed until culture results are available. If symptoms are questionable or mild this is usually a feasible approach. An antimicrobial specific for the infecting organism and susceptibilities may then be selected. Residents with a long-term indwelling catheter who are diagnosed with symptomatic urinary infection should have the catheter replaced and a urine specimen collected through the new catheter before initiation of antimicrobial therapy [33]. In addition to providing a more reliable urine specimen, catheter replacement significantly decreases the time to defervescence and the frequency of early symptomatic relapse after therapy.

Antimicrobial selection

The specific antimicrobial regimen selected is based on the known or presumed site of infection, infecting organism, patient tolerance, renal and hepatic function, and severity of presentation [36]. These principles are similar to those for noninstitutionalized populations of any age. Whenever possible a specific antimicrobial should be selected targeted at a known pathogen. Widespread empiric antimicrobial use should be avoided as it promotes resistance and may limit subsequent therapeutic choices. A conservative approach to selection of an antimicrobial which limits broad-spectrum antimicrobial use as much as possible is suggested by the Society of Healthcare Epidemiology of America (SHEA) guidelines [36]. When any empiric therapy is initiated, the clinical course and relevant microbiology should be reassessed at 48–72 hours to determine whether the regimen should be continued or modified. By this time

any culture results obtained prior to antimicrobial therapy will usually be available and the response to initial management can be assessed.

Most elderly long-term care facility residents with lower respiratory tract infection of mild to moderate severity will be effectively treated in the nursing home with relatively narrow-spectrum antimicrobials, as suggested in the SHEA Long Term Care Committee Guidelines [30]. A strategy of reassessment of pneumonia treatment at 72 hours with expanded coverage at that time if response has been inadequate has been shown to be safe and effective [40]. The IDSA guidelines, however, recommend universal empiric treatment with a fluoroquinolone or amoxicillin-clavulanic acid together with azithromycin or clarithromycin [41]. This initial broad-spectrum coverage is proposed to maximize coverage for all potential pathogens. For the few cases where sputum specimens for culture are obtained, a retreat to more specific therapy may then be possible at 72 hours. These recommendations for uniform broad coverage have not, however, been validated in prospective, randomized clinical trials.

Prevention

Resident interventions

Prevention of infections in long-term care facilities can be considered from both the patient and institutional perspective. General patient measures which are recommended to decrease the risk of infection include maintenance of adequate nutrition and optimal management of comorbid illness. Studies to date, however, report no decrease in the frequency of endemic infections in long-term care facility residents with vitamin or mineral supplements [42,43], although one study reported improved immunologic parameters [44]. These findings suggest nutritional supplements should not be recommended for residents of long-term care facilities in developed countries as a strategy to decrease infections. It is evident that optimal management of comorbid illnesses may prevent some infections. For instance, appropriate management of congestive heart failure to limit pedal edema would decrease the risk for leg infections. Following recommended nursing practices for immobile patients will prevent decubitus ulcers. However, given current standards of practice, whether intensified medical or nursing care can further decrease infections is not known.

The most important specific intervention to prevent infection is yearly influenza vaccination [7]. In a systematic review of the effectiveness of influenza vaccines in elderly people, based on 29 cohort studies in long-term care facilities, immunization with influenza vaccine was found to be 23% effective (95% CI 6–36%) in reducing influenza-like illness when vaccine the match was good, but was not significantly different from no vaccination when the match was poor or unknown [45]. The efficacy of the vaccines against laboratory-confirmed influenza was not significant but there was a large effect of well-matched vaccines in preventing pneumonia (vaccine effectiveness 46%, 95% CI 30–58%), hospital admission for influenza and pneumonia (45%, 95% CI 16–64%), and all-cause mortality (60%, 95% CI 23–79%). Although these findings are more consistent than those in the elderly in the community, where the vaccine was ineffective against influenza-like illness or confirmed influenza but effective against all-cause mortality, concern has been raised about the role of bias in such results [46].

Studies have also repeatedly reported that increased staff vaccination rates are associated with decreased resident mortality during influenza outbreaks [47,48]. Pneumonococcal vaccination is recommended, although clear benefits for residents of long-term care facilities have not been documented [49]. Other specific interventions may be appropriate for selected patients. For instance, prophylaxis with penicillin G or benzathine penicillin G prevents recurrent episodes of erysipelas for residents who experience frequent recurrences, and isoniazid treatment of latent tuberculosis infection prevents reactivation [10].

Infection control

Infection control programs are required for long-term care facilities [50]. The components of these programs include a designated infection control practitioner to oversee and manage the program, and an oversight committee. Specific infection control functions include surveillance of infections, outbreak control, development of infection prevention policies and procedures, education of patients, staff, and visitors with respect to infection prevention, resident and employee health programs to prevent infection,

antibiotic review, and meeting legislated requirements for disease reporting. Local regulations and standards for environmental cleaning, laundry, waste management, and food handling must be met.

Studies have not yet been reported to document the effectiveness of these programs. Specific components have been evaluated in some studies. For instance, handwashing with an alcohol rinse or with soap and water does not influence infection rates [51]. Routine glove use is as effective as contact isolation precautions in limiting transmission of antimicrobial-resistant organisms in long-term care facilities [52]. Evaluation of the effectiveness of infection control programs and individual components of these programs has been identified as a priority for research in long-term care facilities [53].

Even with optimal patient management and facility infection control, outbreaks will occur in long-term care facilities. Ensuring that appropriate policies to respond to outbreaks are established proactively is part of the "emergency preparedness" of any facility. These policies should address general approaches to outbreak management with any infectious agent, as well as specific interventions for common organisms including influenza, other respiratory infections, foodborne outbreaks, norovirus outbreaks, scabies, and group A streptococcus. Effective surveillance and control programs which promptly identify residents who are potentially infectious and support rapid institution of effective control measures early in an outbreak will limit adverse effects for residents, staff, and the facility.

When infection control policies for management of potentially infected residents are developed, recommendations for barrier precautions or isolation to limit transmission must be implemented sparingly. Functionally impaired elderly individuals who have restrictions placed on social or physical activity may experience disorientation and further deterioration in functional status. Thus, restrictions should only be considered when there is clearly a danger to other residents or staff and proposed restrictions are effective in decreasing this risk. The approach may be different from recommendations for acute care facilities. For instance, isolation of elderly nursing home residents with shingles would seldom be indicated. Most facility residents will be seropositive for varicella, and management should be through covering active lesions and glove use by staff members. Similarly, contact precautions do not limit transmission of antimicrobial-resistant organisms, and routine glove use may be a more humane and practical approach [52].

Antimicrobial-resistant organisms

Some long-term care facilities have a high prevalence of antimicrobial-resistant organisms [1,54,55]. MRSA, VRE, and fluoroquinolone-resistant or ESBL-producing gram-negative organisms are of particular concern. The prevalence of resistant organisms is highly variable among facilities, but even in high-prevalence facilities, morbidity attributable to resistant organisms is limited. MRSA and VRE are usually acquired in acute care facilities and introduced into long-term care facilities when residents are transferred, with relatively limited transmission within the facility itself. The approach to preventing transmission of resistant organisms in long-term care facilities is controversial [56]. In the absence of evidence for excess morbidity and mortality, restrictive interventions cannot be advocated. Appropriate hand hygiene should always be followed by staff and residents. In a nonoutbreak situation, restriction of resident participation in social activities, communal dining, or other interactions would not be appropriate solely on the basis of colonization with a resistant organism.

Case presentation (continued)

For the first patient, you diagnose an exacerbation of pulmonary edema and adjust her diuretic medications. Antimicrobials are not initiated, but nursing staff are requested to reassess the patient at 24 and 48 hours. There are no further temperature elevations. Three days later, the urine culture report returns growing *E. coli* $>10^5$ cfu/mL. However, the patient has returned to her previous clinical status. You interpret the positive urine culture as asymptomatic bacteriuria, and no antimicrobial therapy is initiated.

For the second patient, a chest adiograph is requested. Antimicrobial therapy is not initiated, but the patient's temperature, respiratory rate, and mental status are monitored twice daily. The chest radiograph is obtained the next day and the report, available 48 hours after your evaluation, shows a possible infiltrate behind the heart on the left side.

Continued

Case presentation (continued)

The patient has continued to experience temperatures peaking at 38°C daily, and the respiratory rate is now 28. The urine culture has returned growing an *E. coli* $>10^8$, Enterococcus $>10^8$, and *P. mirabilis* $>10^8$. Your assessment, given the tachypnea and sustained fever, is that the patient has a lower respiratory tract infection, and oral antimicrobial therapy is initiated. The urine culture results are interpreted as consistent with the polymicrobial bacteriuria anticipated for a resident with a chronic indwelling catheter. Over the next 72 hours the temperature returns to normal, the respiratory rate decreases, and the nursing staff report the patient has returned to his former status.

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