

Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections

Dennis L. Stevens,^{1,3} Alan L. Bisno,⁵ Henry F. Chambers,^{6,7} E. Dale Everett,¹³ Patchen Dellinger,² Ellie J. C. Goldstein,^{8,9} Sherwood L. Gorbach,¹⁴ Jan V. Hirschmann,^{3,4} Edward L. Kaplan,^{15,16} Jose G. Montoya,^{10,11,12} and James C. Wade¹⁷

¹Infectious Diseases Section, Veterans Affairs Medical Center, Boise, Idaho; ²Department of Surgery, ³University of Washington School of Medicine, and ⁴Seattle Veterans Affairs Medical Center, Seattle, Washington; ⁵University of Miami Miller School of Medicine, Miami, Florida; ⁶Infectious Diseases, San Francisco General Hospital, and ⁷University of California–San Francisco, San Francisco, ⁸R. M. Alden Research Laboratory, Santa Monica, ⁹University of California, Los Angeles School of Medicine, Los Angeles, and ¹⁰Department of Medicine and ¹¹Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine, and ¹²Research Institute, Palo Alto Medical Foundation, Palo Alto, California; ¹³University of Missouri Health Science Center, University of Missouri, Columbia; ¹⁴Tufts University School of Medicine, Boston, Massachusetts; ¹⁵University of Minnesota Medical School and ¹⁶Division of Epidemiology, University of Minnesota School of Public Health, Minneapolis, Minnesota; and ¹⁷Division of Neoplastic Diseases and Related Disorders, Medical College of Wisconsin, Milwaukee, Wisconsin

EXECUTIVE SUMMARY

Soft-tissue infections are common, generally of mild to modest severity, and are easily treated with a variety of agents. An etiologic diagnosis of simple cellulitis is frequently difficult and generally unnecessary for patients with mild signs and symptoms of illness. Clinical assessment of the severity of infection is crucial, and several classification schemes and algorithms have been proposed to guide the clinician [1]. However, most clinical assessments have been developed from either retrospective studies or from an author's own "clinical experience," illustrating the need for prospective studies with defined measurements of severity coupled to management issues and outcomes.

Until then, it is the recommendation of this committee that patients with soft-tissue infection accompanied by signs and symptoms of systemic toxicity (e.g., fever or hypothermia, tachycardia [heart rate, >100 beats/min], and hypotension [systolic blood pressure, <90 mm Hg or 20 mm Hg below baseline]) have blood drawn to determine the following laboratory param-

eters: results of blood culture and drug susceptibility tests, complete blood cell count with differential, and creatinine, bicarbonate, creatine phosphokinase, and C-reactive protein levels. In patients with hypotension and/or an elevated creatinine level, low serum bicarbonate level, elevated creatine phosphokinase level (2–3 times the upper limit of normal), marked left shift, or a C-reactive protein level >13 mg/L, hospitalization should be considered and a definitive etiologic diagnosis pursued aggressively by means of procedures such as Gram stain and culture of needle aspiration or punch biopsy specimens, as well as requests for a surgical consultation for inspection, exploration, and/or drainage. Other clues to potentially severe deep soft-tissue infection include the following: (1) pain disproportionate to the physical findings, (2) violaceous bullae, (3) cutaneous hemorrhage, (4) skin sloughing, (5) skin anesthesia, (6) rapid progression, and (7) gas in the tissue. Unfortunately, these signs and symptoms often appear later in the course of necrotizing infections. In these cases, emergent surgical evaluation is of paramount importance for both diagnostic and therapeutic reasons.

Emerging antibiotic resistance among *Staphylococcus aureus* (methicillin resistance) and *Streptococcus pyogenes* (erythromycin resistance) are problematic, because both of these organisms are common causes of a variety of skin and soft-tissue infections and because empirical choices of antimicrobials must include agents with activity against resistant strains. Minor skin and soft-tissue infections may be empirically treated with semi-

Received 13 July 2005; accepted 14 July 2005; electronically published 14 October 2005.

These guidelines were developed and issued on behalf of the Infectious Diseases Society of America.

Reprints or correspondence: Dr. Dennis L. Stevens, Infectious Disease Section, VAMC, 500 West Fort St. (Bldg. 45), Boise, ID 83702 (dlstevens@mindspring.com).

Clinical Infectious Diseases 2005;41:000–000

© 2005 by the Infectious Diseases Society of America. All rights reserved.
1058-4838/2005/4110-000X\$15.00

synthetic penicillin, first-generation or second-generation oral cephalosporins, macrolides, or clindamycin (A-I); however, 50% of methicillin-resistant *S. aureus* (MRSA) strains have inducible or constitutive clindamycin resistance [2] (table 1). Most community-acquired MRSA strains remain susceptible to trimethoprim-sulfamethoxazole and tetracycline, though treatment failure rates of 21% have been reported in some series with doxycycline or minocycline [3]. Therefore, if patients are sent home receiving these regimens, it is prudent to reevaluate them in 24–48 h to verify a clinical response. Progression despite receipt of antibiotics could be due to infection with resistant microbes or because a deeper, more serious infection exists than was previously realized.

Patients who present to the hospital with severe infection or whose infection is progressing despite empirical antibiotic therapy should be treated more aggressively, and the treatment strategy should be based upon results of appropriate Gram stain, culture, and drug susceptibility analysis. In the case of *S. aureus*, the clinician should assume that the organism is resistant, because of the high prevalence of community-associated MRSA strains, and agents effective against MRSA (i.e., vancomycin, linezolid, or daptomycin) should be used (A-I). Step-down to treatment with other agents, such as tetracycline or trimethoprim-sulfamethoxazole, for MRSA infection may be possible, based on results of susceptibility tests and after an initial clinical response. In the United States, not all laboratories perform susceptibility testing on *S. pyogenes*. However, the Centers for Disease Control and Prevention has provided national surveillance data that suggest a gradual trend of increasing macrolide resistance of *S. pyogenes* from 4%–5% in 1996–1998 to 8%–9% in 1999–2001 [4]. Of interest, 99.5% of strains remain susceptible to clindamycin, and 100% are susceptible to penicillin.

Impetigo, erysipelas, and cellulitis. Impetigo may be caused by infection with *S. aureus* and/or *S. pyogenes*. The

decision of how to treat impetigo depends on the number of lesions, their location (face, eyelid, or mouth), and the need to limit spread of infection to others. The best topical agent is mupirocin (A-I), although resistance has been described [5]; other agents, such as bacitracin and neomycin, are considerably less effective treatments. Patients who have numerous lesions or who are not responding to topical agents should receive oral antimicrobials effective against both *S. aureus* and *S. pyogenes* (A-I) (table 2). Although rare in developed countries (<1 case/1,000,000 population per year), glomerulonephritis following streptococcal infection may be a complication of impetigo caused by certain strains of *S. pyogenes*, but no data demonstrate that treatment of impetigo prevents this sequela.

Classically, erysipelas, is a fiery red, tender, painful plaque with well-demarcated edges and is commonly caused by streptococcal species, usually *S. pyogenes*.

Cellulitis may be caused by numerous organisms that are indigenous to the skin or to particular environmental niches. Cellulitis associated with furuncles, carbuncles, or abscesses is usually caused by *S. aureus*. In contrast, cellulitis that is diffuse or unassociated with a defined portal is most commonly caused by streptococcal species. Important clinical clues to other causes include physical activities, trauma, water contact, and animal, insect, or human bites. In these circumstances appropriate culture material should be obtained, as they should be in patients who do not respond to initial empirical therapy directed against *S. aureus* and *S. pyogenes* and in immunocompromised hosts. Unfortunately, aspiration of skin is not helpful in 75%–80% of cases of cellulitis, and results of blood cultures are rarely positive (<5% of cases).

Penicillin, given either parenterally or orally depending on clinical severity, is the treatment of choice for erysipelas (A-I). For cellulitis, a penicillinase-resistant semisynthetic penicillin or a first-generation cephalosporin should be selected (A-I), unless streptococci or staphylococci resistant to these agents

Table 1. Infectious Diseases Society of America–US Public Health Service Grading System for ranking recommendations in clinical guidelines.

| Category, grade | Definition |
|----------------------------|--|
| Strength of recommendation | |
| A | Good evidence to support a recommendation for use; should always be offered |
| B | Moderate evidence to support a recommendation for use; should generally be offered |
| C | Poor evidence to support a recommendation; optional |
| D | Moderate evidence to support a recommendation against use; should generally not be offered |
| E | Good evidence to support a recommendation against use; should never be offered |
| Quality of evidence | |
| I | Evidence from ≥1 properly randomized, controlled trial |
| II | Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments |
| III | Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees |

are common in the community. For penicillin-allergic patients, choices include clindamycin or vancomycin.

Lack of clinical response could be due to unusual organisms, resistant strains of staphylococcus or streptococcus, or deeper processes, such as necrotizing fasciitis or myonecrosis. In patients who become increasingly ill or experience increasing toxicity, necrotizing fasciitis, myonecrosis, or toxic shock syndrome should be considered, an aggressive evaluation initiated, and antibiotic treatment modified, on the basis of Gram stain results, culture results, and antimicrobial susceptibilities of organisms obtained from surgical specimens.

Necrotizing infections. Necrotizing fasciitis may be monomicrobial and caused by *S. pyogenes*, *Vibrio vulnificus*, or *Aeromonas hydrophila*. Recently, necrotizing fasciitis was described in a patient with MRSA infection [7]. Polymicrobial necrotizing fasciitis may occur following surgery or in patients with peripheral vascular disease, diabetes mellitus, decubitus ulcers, and spontaneous mucosal tears of the gastrointestinal or genitourinary tract (i.e., Fournier gangrene). As with clostridial myonecrosis, gas in the deep tissues is frequently found in these mixed infections.

Gas gangrene is a rapidly progressive infection caused by *Clostridium perfringens*, *Clostridium septicum*, *Clostridium histolyticum*, or *Clostridium novyi*. Severe penetrating trauma or crush injuries associated with interruption of the blood supply are the usual predisposing factors. *C. perfringens* and *C. novyi* infections have recently been described among heroin abusers following intracutaneous injection of black tar heroin. *C. septicum*, a more aerotolerant *Clostridium* species, may cause spontaneous gas gangrene in patients with colonic lesions (such as those due to diverticular disease), adenocarcinoma, or neutropenia.

Necrotizing fasciitis and gas gangrene may cause necrosis of skin, subcutaneous tissue, and muscle. Cutaneous findings of purple bullae, sloughing of skin, marked edema, and systemic toxicity mandate prompt surgical intervention. For severe group A streptococcal and clostridial necrotizing infections, parenteral clindamycin and penicillin treatment is recommended (A-II). A variety of antimicrobials directed against aerobic gram-positive and gram-negative bacteria, as well as against anaerobes, may be used in mixed necrotizing infections (B-II).

Infections following animal or human bites. Animal bites account for 1% of all emergency department visits, and dog bites are responsible for 80% of such cases. Although *Pasteurella* species are the most common isolates, cat and dog bites contain an average of 5 different aerobic and anaerobic bacteria per wound, often including *S. aureus*, *Bacteroides tectum*, and *Fusobacterium*, *Capnocytophaga*, and *Porphyromonas* species. The decision to administer oral or parenteral antibiotics depends on the depth and severity of the wound and on the time since

the bite occurred. Patients not allergic to penicillin should receive treatment with oral amoxicillin-clavulanate or with intravenous ampicillin-sulbactam or ertapenem (B-II), because agents such as dicloxacillin, cephalexin, erythromycin, and clindamycin have poor activity against *Pasteurella multocida*. Although cefuroxime, cefotaxime, and ceftriaxone are effective against *P. multocida*, they do not have good anaerobic spectra. Thus, ceftiofur or carbapenem antibiotics could be used parenterally in patients with mild penicillin allergies. Patients with previous severe reactions can receive oral or intravenous doxycycline, trimethoprim-sulfamethoxazole, or a fluoroquinolone plus clindamycin.

Human bites may occur from accidental injuries, purposeful biting, or closed fist injuries. The bacteriologic characteristics of these wounds are complex but include infection with aerobic bacteria, such as streptococci, *S. aureus*, and *Eikenella corrodens*, as well as with multiple anaerobic organisms, including *Fusobacterium*, *Peptostreptococcus*, *Prevotella*, and *Porphyromonas* species. *E. corrodens* is resistant to first-generation cephalosporins, macrolides, clindamycin, and aminoglycosides. Thus, intravenous treatment with ampicillin-sulbactam or ceftiofur is the best choice (B-III).

Infections associated with animal contact. Infections associated with animal contact, although uncommon, are frequently severe, sometimes lethal, and diagnostically challenging. The potential use of *Bacillus anthracis*, *Francisella tularensis*, and *Yersinia pestis* for bioterrorism has generated great interest in rapid diagnostic techniques, because early recognition and treatment are essential. Doxycycline or ciprofloxacin therapy is recommended in standard doses for nonpregnant adults and children >8 years of age, pending identification of the offending agent (B-III).

Adults and children who receive a diagnosis of tularemia should receive an aminoglycoside, preferably streptomycin or gentamicin, for 7–10 days. In mild cases, doxycycline or tetracycline for 14 days is recommended (B-III) (comments regarding treatment of children <8 years of age are specified in table 3). Patients with bubonic plague should receive streptomycin, tetracycline, or chloramphenicol for 10–14 days and should be placed in isolation for 48 h after initiation of treatment, because some patients may develop secondary pneumonic plague (B-III).

Data regarding antibiotic efficacy for treatment of cat-scratch disease are inconclusive, although 1 small study demonstrated more-rapid lymph node regression in patients receiving azithromycin, compared with patients receiving no treatment. Cutaneous bacillary angiomatosis has not been systematically studied, but treatment with erythromycin or doxycycline in standard doses for 4 weeks has been effective in very small series (B-III).

On the basis of very incomplete data, erysiploid is best

Table 2. Antimicrobial therapy for impetigo and for skin and soft-tissue infections.

| Antibiotic therapy, by disease | Dosage | | Comment |
|-----------------------------------|---|---|---|
| | Adults | Children ^a | |
| Impetigo^b | | | |
| Dicloxacillin | 250 mg 4 times per day po | 12 mg/kg/day in 4 divided doses po | ... |
| Cephalexin | 250 mg 4 times per day po | 25 mg/kg/day in 4 divided doses po | ... |
| Erythromycin | 250 mg 4 times per day po ^c | 40 mg/kg/day in 4 divided doses po | Some strains of <i>Staphylococcus aureus</i> and <i>Streptococcus pyogenes</i> may be resistant |
| Clindamycin | 300–400 mg 3 times per day po | 10–20 mg/kg/day in 3 divided doses po | ... |
| Amoxicillin/clavulanate | 875/125 mg twice per day po | 25 mg/kg/day of the amoxicillin component in 2 divided doses po | ... |
| Mupirocin ointment | Apply to lesions 3 times per day | Apply to lesions 3 times per day | For patients with a limited number of lesions |
| MSSA SSTI | | | |
| Nafcillin or oxacillin | 1–2 g every 4 h iv | 100–150 mg/kg/day in 4 divided doses | Parental drug of choice; inactive against MRSA |
| Cefazolin | 1 g every 8 h iv | 50 mg/kg/day in 3 divided doses | For penicillin-allergic patients, except those with immediate hypersensitivity reactions |
| Clindamycin | 600 mg/kg every 8 h iv or 300–450 mg 3 times per day po | 25–40 mg/kg/day in 3 divided doses iv or 10–20 mg/kg/day in 3 divided doses po | Bacteriostatic; potential of cross-resistance and emergence of resistance in erythromycin-resistant strains; inducible resistance in MRSA |
| Dicloxacillin | 500 mg 4 times per day po | 25 mg/kg/day in 4 divided doses po | Oral agent of choice for methicillin-susceptible strains |
| Cephalexin | 500 mg 4 times per day po | 25 mg/kg/day in 4 divided doses po | For penicillin-allergic patients, except those with immediate hypersensitivity reactions |
| Doxycycline, minocycline | 100 mg twice per day po | Not recommended for persons aged <8 years ^d | Bacteriostatic; limited recent clinical experience |
| TMP-SMZ | 1 or 2 double-strength tablets twice per day po | 8–12 mg/kg (based on the trimethoprim component) in either 4 divided doses iv or 2 divided doses po | Bactericidal; efficacy poorly documented |
| MRSA SSTI | | | |
| Vancomycin | 30 mg/kg/day in 2 divided doses iv | 40 mg/kg/day in 4 divided doses iv | For penicillin-allergic patients; parenteral drug of choice for treatment of infections caused by MRSA |
| Linezolid | 600 mg every 12 h iv or 600 mg twice per day po | 10 mg/kg every 12 h iv or po | Bacteriostatic; limited clinical experience; no cross-resistance with other antibiotic classes; expensive; may eventually replace other second-line agents as a preferred agent for oral therapy of MRSA infections |
| Clindamycin | 600 mg/kg every 8 h iv or 300–450 mg 3 times per day po | 25–40 mg/kg/day in 3 divided doses iv or 10–20 mg/kg/day in 3 divided doses po | Bacteriostatic; potential of cross-resistance and emergence of resistance in erythromycin-resistant strains; inducible resistance in MRSA |
| Daptomycin | 4 mg/kg every 24 h iv | Not applicable | Bactericidal; possible myopathy |
| Doxycycline, minocycline | 100 mg twice per day po | Not recommended for persons aged <8 years ^d | Bacteriostatic, limited recent clinical experience |
| TMP-SMZ | 1 or 2 double-strength tablets twice per day po | 8–12 mg/kg/day (based on the trimethoprim component) in either 4 divided doses iv or 2 divided doses po | Bactericidal; limited published efficacy data |

NOTE. MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; SSTI, skin and soft-tissue infection; TMP-SMZ, trimethoprim-sulfamethoxazole. iv, intravenously; po, orally.

^a Doses listed are not appropriate for neonates. Refer to the report by the Committee on Infectious Diseases, American Academy of Pediatrics [6] for neonatal doses.

^b Infection due to *Staphylococcus* and *Streptococcus* species. Duration of therapy is ~7 days, depending on the clinical response.

^c Adult dosage of erythromycin ethylsuccinate is 400 mg 4 times per day po.

^d See [6] for alternatives in children.

Table 3. Antibiotic therapy for community-acquired and bioterrorism-related cutaneous anthrax.

| Antibiotic therapy, by route of anthrax acquisition | Dosage | |
|--|---|---|
| | Adults | Children ^a |
| Community acquired | | |
| Penicillin V | 200–500 mg po 4 times daily in divided doses | 25–50 mg/kg/day in divided doses 2 or 4 times per day |
| Penicillin G | 8–12 MU/day iv in divided doses every 4–6 h | 100,000–150,000 U/kg/day iv in divided doses every 4–6 h |
| Amoxicillin | 500 mg po every 8 h | Persons who weigh ≤20 kg: 500 mg po every 8 h; persons who weigh <20 kg: 40 mg/kg po in divided doses every 8 h |
| Erythromycin | 250 mg po every 6 h | 40 mg/kg/day in divided doses every 6 h |
| Erythromycin lactobionate | 15–20 mg/kg (4 g maximum) iv in divided doses every 6 h | 20–40 mg/kg/day iv in divided doses every 6 h |
| Tetracycline | 250–500 mg po or iv every 6 h | ... |
| Doxycycline ^b | 100 mg twice per day po or iv | ... |
| Ciprofloxacin ^b | 500 mg twice per day or 400 mg iv every 12 h | ... |
| Bioterrorism or suspected bioterrorism | | |
| Doxycycline ^b | 100 mg twice per day po or iv | Persons who weigh ≤45 kg: 2.2 mg/kg every 12 h; persons who weigh >45 kg: 100 mg twice per day po or iv |
| Ciprofloxacin ^b | 500 mg twice per day | 10–15 mg/kg every 12 h po or iv (not to exceed 1 g in 24 h) |

NOTE. As a rule, the use of fluoroquinolones is contraindicated by the US Food and Drug Administration for children and adolescents <18 years of age. It should also be noted that tetracyclines are rarely used in children <8 years of age. Alternatives should be strongly considered for these 2 antibiotics [6]. iv, intravenously; po, orally.

^a Dosages listed for children are not appropriate for neonates. Refer to the report by the Committee on Infectious Diseases, American Academy of Pediatrics [6] for neonatal dosing regimens.

^b Doxycycline, tetracycline, and ciprofloxacin are not generally recommended during pregnancy or for children <8 years of age, except in exceptional circumstances.

treated with oral penicillin or amoxicillin for 10 days (B-III). *E. rhusiopathiae* is resistant in vitro to vancomycin, teicoplanin, and daptomycin (E-III).

Surgical site infections. Surgical soft-tissue infections include those occurring postoperatively and those severe enough to require surgical intervention for diagnosis and treatment. The algorithm presented clearly indicates that surgical site infection rarely occurs during the first 48 h after surgery, and fever during that period usually arises from non-infectious or unknown causes. In contrast, after 48 h, surgical site infection is a more common source of fever, and careful inspection of the wound is indicated. For patients with a temperature <38.5°C and without tachycardia, observation, dressing changes, or opening the incision site suffices. Patients with a temperature >38.5°C or a heart rate >110 beats/min generally require antibiotics as well as opening of the suture line. Infections developing after surgical procedures involving nonsterile tissue, such as colonic, vaginal, biliary or respiratory mucosa, may be caused by a combination of aerobic and anaerobic bacteria. These infections can rapidly progress and involve deeper structures than just the skin, such as fascia, fat, or muscle (see table 4).

Infections in the immunocompromised host. Skin and soft tissues are common sites of infection in compromised hosts and usually pose major diagnostic challenges for the following 3 reasons: (1) infections are caused by diverse organisms, including organisms not ordinarily considered to be pathogens in otherwise healthy hosts; (2) infection of the soft tissues may

occur as part of a broader systemic infection; and (3) the degree and type of immune deficiency attenuate the clinical findings. The importance of establishing a diagnosis and performing susceptibility testing is crucial, because many infections are hospital acquired, and mounting resistance among both gram-positive and gram-negative bacteria make dogmatic empirical treatment regimens difficult, if not dangerous. In addition, fungal infections may present with cutaneous findings.

Immunocompromised patients who are very ill or experiencing toxicity typically require very broad-spectrum empirical agents that include specific coverage for resistant gram-positive bacteria, such as MRSA (e.g., vancomycin, linezolid, daptomycin, or quinupristin/dalfopristin). Coverage for gram-negative bacteria may include monotherapy with a cephalosporin possessing activity against *Pseudomonas* species, with carbapenems, or with a combination of either a fluoroquinolone or an aminoglycoside plus either an extended-spectrum penicillin or cephalosporin.

Infections in patients with cell-mediated immunodeficiency (such as that due to Hodgkin disease, lymphoma, HIV infection, bone marrow transplantation, and receipt of long-term high-dose immunosuppressive therapy) can be caused by either common or unusual bacteria, viruses, protozoa, helminths, or fungi. Although infection may begin in the skin, cutaneous lesions can also be the result of hematogenous seeding. A well-planned strategy for prompt diagnosis, including biopsy and aggressive treatment protocols, is essential. Diagnostic strategies require laboratory support capable of rapid processing and early

detection of bacteria (including *Mycobacteria* and *Nocardia* species), viruses, and fungi. The algorithm presented provides an approach to diagnosis and treatment. The empirical antibiotic guidelines are based on results of clinical trials, national surveillance antibiograms, and consensus meetings. Because antimicrobial susceptibilities vary considerably across the nation, clinicians must base empirical treatment on the antibiograms in their own location.

Microbiologic cultures are important in establishing a specific diagnosis, and testing the drug susceptibility of organisms is critical for optimal antimicrobial treatment. This guideline offers recommendations for empirical treatment of specific community-acquired and hospital-acquired infections. Nonetheless, therapy may fail for several reasons: (1) the initial diagnosis and/or treatment chosen is incorrect, (2) the etiologic agent from a given locale is resistant to antibiotics, (3) antimicrobial resistance develops during treatment, and (4) the infection is deeper and more complex than originally estimated.

INTRODUCTION

This practice guideline provides recommendations for diagnosis and management of skin and soft-tissue infections in otherwise healthy hosts and compromised hosts of all age groups. These infections have diverse etiologies that depend, in part, on the epidemiological setting. Thus, obtaining a careful history, including information about the patient's immune status, the geographical locale, travel history, recent trauma or surgery, previous antimicrobial therapy, lifestyle, hobbies, and animal exposure or bites is key to developing an adequate differential diagnosis and an appropriate index of suspicion for specific etiological agents. Recognizing the physical examination findings and understanding the anatomical relationships of skin and soft tissue are also crucial for establishing the correct diagnosis. In some cases, this information is insufficient, and biopsy or aspiration of tissue may be necessary. In addition, radiographic procedures may be useful to determine the level of infection and the presence of gas or abscess. Finally, surgical exploration or debridement is an important diagnostic, as well as therapeutic, procedure in immunocompromised hosts or in patients with necrotizing infections or myonecrosis.

Three contemporary problems confounding the clinical evaluation of patients with skin and soft-tissue infection are diagnosis, severity of infection, and pathogen-specific antibiotic resistance patterns. Dozens of microbes may cause soft-tissue infections, and although specific bacteria may cause a particular type of infection, considerable overlaps in clinical presentations exist. Clues to the diagnosis or algorithmic approaches to diagnosis are covered in detail in the text to follow. Specific recommendations for therapy are given, each with a rating that indicates the strength of and evidence for recommendations, expressed using the Infectious Diseases Society of America–US

Table 4. Antibiotic choices for incisional surgical site infections (SSIs).

| Antibiotic therapy for SSIs, by site of operation |
|--|
| Intestinal or genital tract |
| Single agents |
| Cefoxitin |
| Ceftizoxime |
| Ampicillin/sulbactam |
| Ticarcillin/clavulanate |
| Piperacillin/tazobactam |
| Imipenem/cilastatin |
| Meropenem |
| Ertapenem |
| Combination agents |
| Facultative and aerobic activity |
| Fluoroquinolone |
| Third-generation cephalosporin |
| Aztreonam ^a |
| Aminoglycoside |
| Anaerobic activity |
| Clindamycin |
| Metronidazole ^a |
| Chloramphenicol |
| Penicillin agent plus β -lactamase inhibitor |
| Nonintestinal |
| Trunk and extremities away from axilla or perineum |
| Oxacillin |
| First-generation cephalosporin |
| Axillary or perineum |
| Cefoxitin |
| Ampicillin/sulbactam |
| Other single agents as described above for intestinal and genital operations |

^a Do not combine aztreonam with metronidazole, because this combination has no activity against gram-positive cocci.

Public Health Service grading system for ranking recommendations in clinical guidelines (table 1).

IMPETIGO

Impetigo, a skin infection that is common throughout the world, consists of discrete purulent lesions that are nearly always caused by β -hemolytic streptococci and/or *S. aureus*. Impetigo occurs most frequently among economically disadvantaged children in tropical or subtropical regions, but it is also prevalent in northern climates during the summer months [8]. Its peak incidence is among children aged 2–5 years, although older children and adults may also be afflicted [9, 10]. There is no sex predilection, and all races are susceptible.

Prospective studies of streptococcal impetigo have demonstrated that the responsible microorganisms initially colonize the unbroken skin [8], an observation that probably explains the influence of personal hygiene on disease incidence. Skin

colonization with a given streptococcal strain precedes the development of impetiginous lesions by a mean duration of 10 days. Inoculation of surface organisms into the skin by abrasions, minor trauma, or insect bites then ensues. During the course of 2–3 weeks, streptococcal strains may be transferred from the skin and/or impetigo lesions to the upper respiratory tract. In contrast, in patients with staphylococcal impetigo, the pathogens are usually present in the nose before causing cutaneous disease.

Impetigo usually occurs on exposed areas of the body, most frequently the face and extremities. The lesions remain well-localized but are frequently multiple and may be either bullous or nonbullous in appearance. Bullous lesions appear initially as superficial vesicles that rapidly enlarge to form flaccid bullae filled with clear yellow fluid, which later becomes darker, more turbid, and sometimes purulent. The bullae may rupture, often leaving a thin brown crust resembling lacquer [11]. The lesions of nonbullous impetigo begin as papules that rapidly evolve into vesicles surrounded by an area of erythema and then become pustules that gradually enlarge and break down over a period of 4–6 days to form characteristic thick crusts. The lesions heal slowly and leave depigmented areas. A deeply ulcerated form of impetigo is known as ecthyma. Although regional lymphadenitis may occur, systemic symptoms are usually absent.

Bullous impetigo is caused by strains of *S. aureus* that produce a toxin causing cleavage in the superficial skin layer. In the past, nonbullous lesions were usually caused by streptococci. Now, most cases are caused by staphylococci alone or in combination with streptococci [12, 13]. Streptococci isolated from lesions are primarily group A organisms, but occasionally, other serogroups (such as C and G) are responsible.

Assays of streptococcal antibodies are of no value in the diagnosis and treatment of impetigo, but they provide helpful supporting evidence of recent streptococcal infection in patients suspected of having poststreptococcal glomerulonephritis. The anti-streptolysin O response is weak in patients with streptococcal impetigo [14, 15], presumably because skin lipids suppress streptolysin O response [16], but anti-DNAse B levels are consistently elevated [14, 15].

In the past, therapy directed primarily at group A streptococci (e.g., penicillin) was successful, both in healing the lesions and decreasing recurrences of nonbullous impetigo for at least several weeks [17, 18]. Because *S. aureus* currently accounts for most cases of bullous impetigo, as well as for a substantial portion of nonbullous infections [13, 19, 20], penicillinase-resistant penicillins or first-generation cephalosporins are preferred (A-I), although impetigo caused by MRSA is increasing in frequency [13] (table 2). Erythromycin has been a mainstay of pyoderma therapy, but its utility may be lessened in areas where erythromycin-resistant strains of *S. aureus*, or more re-

cently, *S. pyogenes*, are prevalent. Topical therapy with mupirocin is equivalent to oral systemic antimicrobials [21, 22] (A-I) and may be used when lesions are limited in number. It is expensive, however, and some strains of staphylococci are resistant [5]. Suppurative complications of streptococcal impetigo are uncommon, and for as yet unexplained reasons, rheumatic fever has never occurred after streptococcal impetigo. On the other hand, cutaneous infections with nephritogenic strains of group A streptococci are the major antecedent of poststreptococcal glomerulonephritis in many areas of the world. No conclusive data indicate that treatment of streptococcal pyoderma prevents nephritis [23], but such therapy is important as an epidemiologic measure in eradicating nephritogenic strains from the community.

ABSCESSSES, CELLULITIS, AND ERYSIPELAS

Cutaneous abscesses. Cutaneous abscesses are collections of pus within the dermis and deeper skin tissues. They are usually painful, tender, and fluctuant red nodules, often surmounted by a pustule and surrounded by a rim of erythematous swelling. Cutaneous abscesses are typically polymicrobial, containing bacteria that constitute the normal regional skin flora, often combined with organisms from adjacent mucous membranes [24–30]. *S. aureus* is present, usually as a single pathogen, in only ~25% of cutaneous abscesses overall. Epidermoid cysts, often erroneously labeled “sebaceous cysts,” ordinarily contain skin flora in the cheesy keratinous material, even when uninflamed. Cultures of inflamed cysts also yield the same organisms, suggesting that the inflammation and purulence occur as a reaction to rupture of the cyst wall and extrusion of its contents into the dermis, rather than as an infectious complication [31].

Effective treatment of abscesses and inflamed epidermoid cysts entails incision, thorough evacuation of the pus, and probing the cavity to break up loculations (A-I). Simply covering the surgical site with a dry dressing is usually the easiest and most effective treatment of the wound [32, 33], although some clinicians pack it with gauze or suture it closed. Gram stain, culture, and systemic antibiotics are rarely necessary (E-III). Unusual exceptions include the presence of multiple lesions, cutaneous gangrene, severely impaired host defenses, extensive surrounding cellulitis, or severe systemic manifestations of infection, such as high fever.

Furuncles and carbuncles. Furuncles (or “boils”) are infections of the hair follicle, usually caused by *S. aureus*, in which suppuration extends through the dermis into the subcutaneous tissue, where a small abscess forms. They differ, therefore, from folliculitis, in which inflammation is more superficial and pus is present in the epidermis. Furuncles can occur anywhere on hairy skin. Each lesion consists of an inflammatory nodule and an overlying pustule through which hair emerges. When in-

fection extends to involve several adjacent follicles, producing a coalescent inflammatory mass with pus draining from multiple follicular orifices, the lesion is called a carbuncle. Carbuncles tend to develop on the back of the neck and are especially likely to occur in diabetic persons.

For small furuncles, moist heat, which seems to promote drainage, is satisfactory. Larger furuncles and all carbuncles require incision and drainage. Systemic antibiotics are usually unnecessary, unless extensive surrounding cellulitis or fever occurs (E-III). Outbreaks of furunculosis caused by MSSA, as well as by MRSA, may occur in families and other settings involving close personal contact (e.g., prisons), especially when skin injury is common, such as sports teams or outdoor recreation groups [34–36]. Inadequate personal hygiene and exposure to others with furuncles are important predisposing factors in these settings. In some cases, fomites may harbor the organism and facilitate transmission of the infection. Depending on the individual circumstances, control of outbreaks may require bathing with antibacterial soaps, such as chlorhexidine; thorough laundering of clothing, towels, and bed wear; separate use of towels and washcloths; and attempted eradication of staphylococcal carriage among colonized persons [36] (B-III).

Some individuals have repeated attacks of furunculosis. A few of these persons, particularly children, have abnormal systemic host responses, but for most, the only identifiable predisposing factor is the presence of *S. aureus* in the anterior nares or, occasionally, elsewhere, such as the perineum [37]. The prevalence of nasal staphylococcal colonization in the general population is 20%–40%, but why some carriers develop recurrent skin infections and others do not is usually unclear.

The major method of controlling recurrent furunculosis is the use of antibacterial agents to eradicate staphylococcal carriage. For persons with nasal colonization, one approach is the application of mupirocin ointment twice daily in the anterior nares for the first 5 days each month [38] (A-I). This regimen reduces recurrences by ~50%. Few systemic antibiotics attain adequate levels in the nasal secretions to achieve protracted elimination of staphylococci [39]. Clindamycin is an exception, and probably the best program for recurrent furunculosis caused by susceptible *S. aureus* is a single oral daily dose of 150 mg of this agent for 3 months, which decreases subsequent infections by ~80% [40] (A-I).

Cellulitis and erysipelas. These terms refer to diffuse, spreading skin infections, excluding infections associated with underlying suppurative foci, such as cutaneous abscesses, necrotizing fasciitis, septic arthritis, and osteomyelitis. Unfortunately, physicians use the words “cellulitis” and “erysipelas” inconsistently. For some, the distinction between the 2 terms relates to the depth of inflammation: erysipelas affects the upper dermis, including the superficial lymphatics, whereas cellulitis involves the deeper dermis, as well as subcutaneous fat. In

practice, however, distinguishing between cellulitis and erysipelas clinically may be difficult, and some physicians, especially in northern Europe, use the term “erysipelas” to describe both infections.

Erysipelas is distinguished clinically from other forms of cutaneous infection by the following 2 features: the lesions are raised above the level of the surrounding skin, and there is a clear line of demarcation between involved and uninvolved tissue [41]. This disorder is more common among infants, young children, and older adults. It is almost always caused by β -hemolytic streptococci (usually group A), but similar lesions can be caused by streptococci from serogroups C or G. Rarely, group B streptococci or *S. aureus* may be involved. In older reports, erysipelas characteristically involved the butterfly area of the face, but at present, the lower extremities are more frequently affected [42, 43].

With early diagnosis and proper treatment, the prognosis is excellent. Rarely, however, the infection may extend to deeper levels of the skin and soft tissues. Penicillin, given either parenterally or orally depending on clinical severity, is the treatment of choice (A-III). If staphylococcal infection is suspected, a penicillinase-resistant semisynthetic penicillin or a first-generation cephalosporin should be selected [44] (A-III). In a randomized, prospective multicenter trial [45], the efficacy of roxithromycin, a macrolide antimicrobial, was equivalent to that for penicillin. Macrolide resistance among group A streptococci, however, is increasing in the United States [46, 47].

Cellulitis is an acute spreading infection of the skin, extending more deeply than erysipelas to involve the subcutaneous tissues. It therefore lacks the distinctive anatomical features described above for erysipelas. Although most cellulitis is caused by β -hemolytic streptococci, a number of other microorganisms may give rise to this disorder (see below).

Both erysipelas and cellulitis are manifested clinically by rapidly spreading areas of edema, redness, and heat, sometimes accompanied by lymphangitis and inflammation of the regional lymph nodes. The skin surface may resemble an orange peel (i.e., *peau d'orange*) because superficial cutaneous edema surrounds the hair follicles, which causes dimpling in the skin because they remain tethered to the underlying dermis. Vesicles, bullae, and cutaneous hemorrhage in the form of petechiae or ecchymoses may develop on the inflamed skin. Systemic manifestations are usually mild, but fever, tachycardia, confusion, hypotension, and leukocytosis are sometimes present and may even occur hours before the skin abnormalities appear. Vesicles and bullae filled with clear fluid are common. Petechiae and ecchymoses may develop in inflamed skin; if these are widespread and associated with systemic toxicity, a deeper infection such as necrotizing fasciitis should be considered.

These infections arise when organisms enter through breaches in the skin. Predisposing factors for these infections

include conditions that make the skin more fragile or local host defenses less effective, such as obesity, previous cutaneous damage, and edema from venous insufficiency or lymphatic obstruction or other causes [48]. The origin of the disrupted cutaneous barrier may be trauma, preexisting skin infections such as impetigo or ecthyma, ulceration, fissured toe webs from maceration or fungal infection, and inflammatory dermatoses, such as eczema. Often, however, the breaks in the skin are small and clinically inapparent. These infections can occur at any location but are most common on the lower legs.

Surgical procedures that increase the risk for cellulitis, presumably due to disruption of lymphatic drainage, include saphenous venectomy [49, 50], axillary node dissection for breast cancer [51, 52], and operations for gynecologic malignancies that involve lymph node dissection, especially when followed by radiation therapy, such as radical vulvectomy and radical hysterectomy [53, 54].

Blood culture results are positive in $\leq 5\%$ of cases [55]. Results of culture of needle aspirations of the inflamed skin are bewilderingly variable, varying from $\leq 5\%$ to $\sim 40\%$ in reported series [56–63], and probably depending on the patient population, the definition of cellulitis, the inclusion or exclusion of cases with associated abscesses, and the determination of whether isolates are pathogens or contaminants. Culture of punch biopsy specimens yields an organism in 20%–30% of cases [57, 64], but the concentration of bacteria is usually quite low [64]. Culture of these specimens, as well as other available evidence, including serologic studies [42, 59, 65] and techniques employing immunofluorescent antibodies to detect antigens in skin biopsy specimens [66, 67], indicate that most of the infections arise from streptococci, often group A, but also from other groups, such as B, C, or G. The source of the pathogens is frequently unclear, but in many infections of the lower extremities, the responsible streptococci are present in the macerated or fissured interdigital toe spaces [68, 69], emphasizing the importance of detecting and treating tinea pedis and other causes of toe web abnormalities in these patients. Occasionally, the reservoir of streptococci is the anal canal [70] or the vagina, especially for group B streptococci causing cellulitis in patients with previous gynecologic cancer treated with surgery and radiation therapy. *S. aureus* less frequently causes cellulitis, often associated with previous penetrating trauma, including injection sites of illicit drug use.

Many other infectious agents can produce cellulitis, but usually only in special circumstances. With cat or dog bites, for example, the organism responsible is typically *Pasteurella* species, especially *P. multocida*, or *Capnocytophaga canimorsus*. *A. hydrophila* may cause cellulitis following immersion in fresh water, whereas infection after saltwater exposure can arise from *Vibrio* species, particularly *V. vulnificus* in warm climates. In rare cases, *Streptococcus iniae* or *E. rhusiopathiae* may cause

infection in persons employed in aquaculture or meatpacking, respectively. Periorbital cellulitis due to *Haemophilus influenzae* can occur in children. Diagnostic and therapeutic considerations of this infection have been reported by the Committee on Infectious Diseases, American Academy of Pediatrics [6]. In neutropenic hosts, infection may be due to *Pseudomonas aeruginosa* or other gram-negative bacilli, and in patients infected with HIV, the responsible organism may be *Helicobacter cinaedi* [71]. Occasionally, *Cryptococcus neoformans* causes cellulitis in patients with deficient cell-mediated immunity.

Because of their very low yield, blood cultures are not fruitful for the typical case of erysipelas or cellulitis, unless it is particularly severe [55]. Needle aspirations and skin biopsies are also unnecessary in typical cases, which should respond to antibiotic therapy directed against streptococci and staphylococci. These procedures may be more rewarding [56] for patients with diabetes mellitus, malignancy, and unusual predisposing factors, such as immersion injury, animal bites, neutropenia, and immunodeficiency.

Diseases sometimes confused with cellulitis include acute dermatitis, such as that due to contact with an allergen; gout, with marked cutaneous inflammation extending beyond the joint involved; and herpes zoster. Acute lipodermatosclerosis, a panniculitis that occurs predominantly in obese women with lower extremity venous insufficiency, causes painful, erythematous, tender, warm, indurated, and sometimes scaly areas in the medial leg that resemble cellulitis [72].

Therapy for the typical case of erysipelas or cellulitis should include an antibiotic active against streptococci. Many clinicians choose an agent that is also effective against *S. aureus*, although this organism rarely causes cellulitis unless associated with an underlying abscess or penetrating trauma. A large percentage of patients can receive oral medications from the start [73]. Suitable agents include dicloxacillin, cephalexin, clindamycin, or erythromycin, unless streptococci or staphylococci resistant to these agents are common in the community (A-I).

Macrolide resistance among group A streptococci has increased regionally in the United States. For parenteral therapy, which is indicated for severely ill patients or for those unable to tolerate oral medications, reasonable choices include a penicillinase-resistant penicillin such as nafcillin, a first-generation cephalosporin such as cefazolin, or, for patients with life-threatening penicillin allergies, clindamycin or vancomycin (A-I). In cases of uncomplicated cellulitis, 5 days of antibiotic treatment is as effective as a 10-day course [74].

Antibiotic treatment alone is effective in most patients with cellulitis. However, patients who are slow to respond may have a deeper infection or underlying conditions, such as diabetes, chronic venous insufficiency, or lymphedema. In some patients, cutaneous inflammation sometimes worsens after initiating therapy, probably because the sudden destruction of pathogens

releases potent enzymes that increase local inflammation. In a single randomized, double-blind, placebo-controlled trial, systemic corticosteroids attenuated this reaction and hastened resolution [75]. Specifically, 108 patients with a diagnosis of uncomplicated erysipelas were randomized to receive antibiotics (90% received benzyl penicillin) plus either an 8-day tapering oral course of corticosteroid therapy beginning with 30 mg of prednisolone or a placebo. Subjects <18 years of age, diabetic patients, and pregnant women were excluded. One-third of enrolled subjects had a previous episode of erysipelas at the current site of infection. Median healing time, median treatment time with intravenous antibiotics, and median duration of hospital stay were all shortened by 1 day in the prednisolone-treated group [75]. Long-term follow-up of these patients showed no difference in relapse or recurrence [76]. Further studies are warranted, but in the meantime, clinicians may wish to consider systemic corticosteroids as an optional adjunct for treatment of uncomplicated cellulitis and erysipelas in selected adult patients.

Elevation of the affected area, an important and often neglected aspect of treatment, quickens improvement by promoting gravity drainage of the edema and inflammatory substances. Patients should also receive appropriate therapy for any underlying condition that may have predisposed to the infection, such as tinea pedis, venous eczema (“stasis dermatitis”), or trauma.

Each attack of cellulitis causes lymphatic inflammation and possibly some permanent damage. Severe or repeated episodes of cellulitis may lead to lymphedema, sometimes substantial enough to cause elephantiasis. Measures to reduce recurrences of cellulitis include treating interdigital maceration, keeping the skin well hydrated with emollients to avoid dryness and cracking, and reducing any underlying edema by such methods as elevation of the extremity, compressive stockings or pneumatic pressure pumps, and, if appropriate, diuretic therapy. If frequent infections occur despite such measures, prophylactic antibiotics appear reasonable; however, published results demonstrating efficacy have been mixed [77–80]. Because streptococci cause most recurrent cellulitis, options include monthly intramuscular benzathine penicillin injections of 1.2 MU in adults or oral therapy with twice-daily doses of either 250 mg of erythromycin or 1 g of penicillin V (B-II). An alternative, but untested, option for reliable patients with recurrent cellulitis is to try to shorten each episode by providing oral antibiotics for them to initiate therapy as soon as symptoms of infection begins. One trial of oral selenium demonstrated a reduced recurrence rate of erysipelas in secondary lymphedema by 80% [81]. This report requires independent confirmation.

Soft-tissue infections and the evaluation of MRSA infection. An emerging problem is the increasing prevalence of skin and

soft-tissue infections caused by community-acquired MRSA. Traditionally regarded as a nosocomial pathogen, MRSA isolates causing community-onset disease differ from their hospital counterparts in several ways [82–84]. Community strains cause infections in patients lacking typical risk factors, such as hospital admission or residence in a long-term care facility; they are often susceptible to non- β -lactam antibiotics, including doxycycline, clindamycin, trimethoprim-sulfamethoxazole, fluoroquinolones, or rifampin; genotypically, they appear not to be related to local hospital strains and to contain type IV *SCCmec* cassette not typical of hospital isolates [85, 86]. Finally, community isolates have frequently contained genes for Panton-Valentine leukocidin [87], which has been associated with mild to severe skin and soft-tissue infections [7]. Outbreaks caused by community-acquired MRSA isolates have occurred among prison and jail inmates, injection drug users, Native American populations, gay men, participants in contact sports, and children [88, 89]. Thus, recurrent or persistent furuncles and impetigo, particularly in these high-risk groups, that do not respond to oral β -lactam antibiotic therapy are increasingly likely to be caused by MRSA. Such lesions should be cultured and antibiotic susceptibilities determined. Fluctuant lesions should be drained. An oral agent to which the isolate is susceptible should be used as initial therapy (table 2). Most community-acquired strains are susceptible to doxycycline or minocycline, but these should be avoided in children ≤ 8 years old and during pregnancy. Clindamycin has excellent antistaphylococcal activity, but there is the potential for emergence of resistance with high-inoculum infections caused by strains inducibly resistant to erythromycin. Linezolid, daptomycin, and vancomycin have excellent efficacy in skin and soft-tissue infections in general and against those due to MRSA specifically [90, 91] (A-I). However, these agents should be reserved for patients who have severe infections requiring hospitalization or who have not responded to attempts to eradicate the infection. Trimethoprim-sulfamethoxazole has been used to treat serious staphylococcal infections, including those due to MRSA. In one double-blind, randomized trial in which 47% of the isolates were MRSA, cures were documented in 37 of the 43 patients receiving trimethoprim-sulfamethoxazole, compared with 57 of 58 patients in the vancomycin group; trimethoprim-sulfamethoxazole failures occurred mostly in patients with MSSA infections [92]. If a fluoroquinolone is chosen, one with enhanced activity against gram-positive bacteria should be used (e.g., levofloxacin, gatifloxacin, or moxifloxacin), but still there is the possibility of emergence of resistance.

NECROTIZING SKIN AND SOFT-TISSUE INFECTIONS

Necrotizing skin and soft-tissue infections differ from the milder, superficial infections by clinical presentation, coexisting

systemic manifestations, and treatment strategies [93, 94]. They are often deep and devastating. They are deep because they may involve the fascial and/or muscle compartments; they are devastating because they cause major destruction of tissue and can lead to a fatal outcome. These conditions are usually “secondary” infections, in that they develop from an initial break in the skin related to trauma or surgery. They can be monomicrobial (usually involving streptococci or, rarely, staphylococci) or polymicrobial (involving a mixed aerobe-anaerobe bacterial flora). Although many specific variations of necrotizing soft-tissue infections have been described on the basis of etiology, microbiology, and specific anatomic location of the infection, the initial approach to the diagnosis, antimicrobial treatment, and decision to use operative management are similar for all forms and are more important than determining the specific variant.

In the initial phases, distinguishing between a cellulitis that should respond to antimicrobial treatment alone and a necrotizing infection that requires operative intervention may be difficult. Several clinical features suggest the presence of a necrotizing infection of the skin and its deeper structures: (1) severe, constant pain; (2) bullae, related to occlusion of deep blood vessels that traverse the fascia or muscle compartments; (3) skin necrosis or ecchymosis (bruising) that precedes skin necrosis; (4) gas in the soft tissues, detected by palpation or imaging; (5) edema that extends beyond the margin of erythema; (6) cutaneous anesthesia; (7) systemic toxicity, manifested by fever, leukocytosis, delirium, and renal failure; and (8) rapid spread, especially during antibiotic therapy. Bullae alone are not diagnostic of deep infections, because they also occur with erysipelas, cellulitis, scalded skin syndrome, disseminated intravascular coagulation, purpura fulminans, some toxins (e.g., those associated with bite from a brown-recluse spider), and primary dermatologic conditions.

Necrotizing Fasciitis

Necrotizing fasciitis is a relatively rare subcutaneous infection that tracks along fascial planes and extends well beyond the superficial signs of infection, such as erythema and other skin changes [95, 96]. The term fasciitis sometimes leads to the mistaken impression that the muscular fascia or aponeurosis is involved. The fascia most commonly referred to is the superficial fascia, which is comprised of all of the tissue between the skin and underlying muscles (i.e., subcutaneous tissue).

Clinical features. Extension from a skin lesion is seen in 80% of cases. The initial lesion, such as a minor abrasion, insect bite, injection site (in the case of drug addicts), or boil, often is trivial. Rare cases have arisen in Bartholin gland abscess or perianal abscess, from which the infection spreads via fascial planes of the perineum, thigh, groin, and abdomen. The remaining 20% of patients have no visible skin lesion. The initial

presentation is that of cellulitis, which can advance rapidly or slowly. As it progresses, there is systemic toxicity with high temperatures. The patient may be disoriented and lethargic. The local site shows the following features: cellulitis (90% of cases), edema (80%), skin discoloration or gangrene (70%), and anesthesia of involved skin (frequent, but the true incidence is unknown).

A distinguishing clinical feature is the wooden-hard feel of the subcutaneous tissues. In cellulitis or erysipelas the subcutaneous tissues can be palpated and are yielding. But in fasciitis, the underlying tissues are firm, and the fascial planes and muscle groups cannot be discerned by palpation. It is often possible to observe a broad erythematous tract in the skin along the route of the infection as it advances cephalad in an extremity. If there is an open wound, probing the edges with a blunt instrument permits ready dissection of the superficial fascial planes well beyond the wound margins.

Bacteriologic characteristics. In the monomicrobial form, the pathogens are *S. pyogenes*, *S. aureus*, *V. vulnificus*, *A. hydrophila*, and anaerobic streptococci (i.e., *Peptostreptococcus* species). Staphylococci and hemolytic streptococci can occur simultaneously. Most infections are community acquired and present in the limbs, with approximately two-thirds of cases in the lower extremities. There is often an underlying cause, such as diabetes, arteriosclerotic vascular disease, or venous insufficiency with edema. Sometimes, a chronic vascular ulcer changes into a more acute process. Cases of necrotizing fasciitis that arise after varicella or trivial injuries, such as minor scratches and insect bites, are almost always due to *S. pyogenes*. The mortality in this group is high, approaching 50%–70% in patients with hypotension and organ failure [97, 98].

In the polymicrobial form, up to 15 different anaerobic and aerobic organisms can be cultured from the involved fascial plane, with an average of 5 pathogens in each wound. Most of the organisms originate from the bowel flora (e.g., coliforms and anaerobic bacteria).

The polymicrobial necrotizing infection is associated with 4 clinical settings: (1) surgical procedures involving the bowel or penetrating abdominal trauma, (2) decubitus ulcer or a perianal abscess, (3) at the site of injection in injection drug users, and (4) spread from a Bartholin abscess or a minor vulvovaginal infection. Although mixed infections are usually noted in this latter setting, some cases are caused by a single pathogen, particularly anaerobic *Streptococcus* species.

Diagnosis. It may not be possible to diagnose fasciitis upon first seeing the patient. Overlying cellulitis is a frequent accompaniment. That the process involves the deeper tissue planes is suggested by the following features: (1) failure to respond to initial antibiotic therapy; (2) the hard, wooden feel of the subcutaneous tissue, extending beyond the area of apparent skin

involvement; (3) systemic toxicity, often with altered mental status; (4) bullous lesions; and (5) skin necrosis or ecchymoses.

CT scan or MRI may show edema extending along the fascial plane. In practice, clinical judgment is the most important element in diagnosis. Data regarding the sensitivity and specificity of CT or MRI are unavailable, and requesting such studies may delay definitive diagnosis and treatment. The most important diagnostic feature of necrotizing fasciitis is the appearance of the subcutaneous tissues or fascial planes at operation. Upon direct inspection, the fascia is swollen and dull gray in appearance, with stringy areas of necrosis. A thin, brownish exudate emerges from the wound. Even during deep dissection, there is typically no true pus. Extensive undermining of surrounding tissues is present, and the tissue planes can be dissected with a gloved finger or a blunt instrument. A Gram stain of the exudate demonstrates the presence of the pathogens and provides an early clue to therapy. Gram-positive cocci in chains suggest *Streptococcus* organisms (either group A or anaerobic). Large gram-positive cocci in clumps suggest *S. aureus*, but this is an unusual primary organism in these spreading infections. Samples for culture are best obtained from the deep tissues. If the infection originated from a contaminated skin wound, such as a vascular ulcer, the bacteriologic characteristics of the superficial wound are not necessarily indicative of deep-tissue infection. Direct needle aspiration of the advancing edge as a means of obtaining material for culture can be helpful if fluid is obtained. A definitive bacteriologic diagnosis is best established by culture of tissue specimens obtained during operation or by positive blood culture results. In doubtful cases, the surgical procedure may provide both diagnosis and treatment. If necrotizing infection is suspected but not confirmed, a small, exploratory incision should be made in the area of maximum suspicion. If a necrotizing infection is present, it will be obvious from the findings described above. If there is no necrosis on exploratory incision, the procedure can be terminated with very little risk or morbidity to the patient. Some have suggested biopsy for frozen section analysis to make the diagnosis. However, if enough suspicion exists to do a biopsy, the diagnosis is usually evident to gross inspection without histological slides.

Treatment. Surgical intervention is the major therapeutic modality in cases of necrotizing fasciitis (A-III). Many cases of necrotizing fasciitis, however, probably begin as cellulitis, and if necrotizing fasciitis is recognized early and treated aggressively, some patients may avoid potentially mutilating surgical procedures. The decision to undertake aggressive surgery should be based on several considerations. First, no response to antibiotics after a reasonable trial is the most common index. A response to antibiotics should be judged by reduction in fever and toxicity and lack of advancement. Second, profound

toxicity, fever, hypotension, or advancement of the skin and soft-tissue infection during antibiotic therapy is an indication for surgical intervention. Third, when the local wound shows any skin necrosis with easy dissection along the fascia by a blunt instrument, more complete incision and drainage are required. Fourth, any soft-tissue infection accompanied by gas in the affected tissue suggests necrotic tissue and requires operative drainage and/or debridement.

Most patients with necrotizing fasciitis should return to the operating room 24–36 h after the first debridement and daily thereafter until the surgical team finds no further need for debridement. Although discrete pus is usually absent, these wounds can discharge copious amounts of tissue fluid; aggressive administration of fluid is a necessary adjunct.

Antimicrobial therapy must be directed at the pathogens and used in appropriate doses (table 5) until repeated operative procedures are no longer needed, the patient has demonstrated obvious clinical improvement, and fever has been absent for 48–72 h. Treatment of polymicrobial necrotizing fasciitis must include agents effective against both aerobes and anaerobes (table 5). In general, ampicillin is useful for coverage of susceptible enteric aerobic organisms, such as *E. coli*, as well as for gram-positive organisms, such as *Peptostreptococcus* species, group B, C, or G streptococci, and some anaerobes (A-III). Clindamycin is useful for coverage of anaerobes and aerobic gram-positive cocci, including most *S. aureus* serogroups. Metronidazole has the greatest anaerobic spectrum against the enteric gram-negative anaerobes, but it is less effective against the gram-positive anaerobic cocci. Gentamicin or a fluorinated quinolone, ticarcillin-clavulanate, or piperacillin-sulbactam is useful for coverage against resistant gram-negative rods. Thus, the best choice of antibiotics for community-acquired mixed infections is a combination of ampicillin-sulbactam plus clindamycin plus ciprofloxacin (A-III).

Necrotizing fasciitis and/or streptococcal toxic shock syndrome caused by group A streptococci should be treated with clindamycin and penicillin (A-II). The rationale for clindamycin is based on in vitro studies demonstrating both toxin suppression and modulation of cytokine (i.e., TNF) production, on animal studies demonstrating superior efficacy versus that of penicillin, and on 2 observational studies demonstrating greater efficacy for clindamycin than for β -lactam antibiotics [99, 100]. Penicillin should be added because of the increasing resistance of group A streptococci to macrolides, although in the United States, only 0.5% of macrolide-resistant group A streptococci are also clindamycin resistant.

A recommendation to use intravenous γ -globulin (IVIG) to treat streptococcal toxic shock syndrome cannot be made with certainty (B-II). Although there is ample evidence for the role of extracellular streptococcal toxins in shock, organ failure, and

Table 5. Treatment of necrotizing infections of the skin, fascia, and muscle.

| First-line antimicrobial agent, by infection type | Adult dosage | Antimicrobial agent(s) for patients with severe penicillin hypersensitivity |
|--|---|---|
| Mixed infection | | |
| Ampicillin-sulbactam or piperacillin-tazobactam plus clindamycin plus ciprofloxacin | 1.5–3.0 g every 6–8 h iv 3.37 g every 6–8 h iv 600–900 mg/kg every 8 h iv 400 mg every 12 h iv | Clindamycin or metronidazole ^a with an aminoglycoside or fluoroquinolone |
| Imipenem/cilastatin | 1 g every 6–8 h iv | ... |
| Meropenem | 1 g every 8 h iv | ... |
| Ertapenem | 1 g every day iv | ... |
| Cefotaxime plus metronidazole or clindamycin | 2 g every 6 h iv 500 mg every 6 h iv 600–900 mg/kg every 8 h iv | ... |
| Streptococcus infection | | |
| Penicillin plus clindamycin | 2–4 MU every 4–6 h iv (adults) 600–900 mg/kg every 8 h iv | Vancomycin, linezolid, quinupristin/dalfopristin, or daptomycin |
| S. aureus infection | | |
| Nafcillin | 1–2 g every 4 h iv | Vancomycin, linezolid, quinupristin/dalfopristin, daptomycin |
| Oxacillin | 1–2 g every 4 h iv | ... |
| Cefazolin | 1 g every 8 h iv | ... |
| Vancomycin (for resistant strains) | 30 mg/kg/day in 2 divided doses iv | ... |
| Clindamycin | 600–900 mg/kg every 8 h iv | Bacteriostatic; potential of cross-resistance and emergence of resistance in erythromycin-resistant strains; inducible resistance in methicillin-resistant <i>S. aureus</i> |
| Clostridium infection | | |
| Clindamycin | 600–900 mg/kg every 8 h iv | ... |
| Penicillin | 2–4 MU every 4–6 h iv | ... |

^a If *Staphylococcus* infection is present or suspected, add an appropriate agent. iv, intravenously.

tissue destruction, different batches of IVIG contain variable quantities of neutralizing antibodies to some of these toxins, and definitive clinical data are lacking [101]. One observational study demonstrated better outcomes in patients receiving IVIG, but these patients were more likely to have had surgery and to have received clindamycin than were historical control subjects [102]. A second study, which was a double-blind, placebo-controlled trial from northern Europe, showed no statistically significant improvement in survival, and, specific to this section, no reduction in the time to no further progression of necrotizing fasciitis (69 h for the IVIG group, compared with 36 h for the placebo group) [103]. Results of these studies provide some promise. However, this committee believes that additional studies of the efficacy of IVIG are necessary before a recommendation can be made regarding use of IVIG for treatment of streptococcal toxic shock syndrome.

Anaerobic Streptococcal Myositis

Anaerobic streptococci cause a more indolent infection than other streptococci. Unlike other necrotizing infections, infection of the muscle and fascial planes by anaerobic streptococci usually is associated with trauma or a surgical procedure.

Incision and drainage are critical. Necrotic tissue and debris are resected but the inflamed, viable muscle should not be removed, because it can heal and regain function. The incision should be packed with moist dressings. Antibiotic treatment is highly effective. These organisms are all susceptible to penicillin or ampicillin, which should be administered in high doses.

Pyomyositis

Pyomyositis, which is caused mainly by *S. aureus*, is the presence of pus within individual muscle groups. Occasionally, *S.*

pneumoniae or a gram-negative enteric bacillus is responsible. Blood culture results are positive in 5%–30% of cases. Because of its geographical distribution, this condition is often called “tropical pyomyositis,” but cases are increasingly recognized in temperate climates, especially in patients with HIV infection or diabetes [104]. Presenting findings are localized pain in a single muscle group, muscle spasm, and fever. The disease occurs most often in an extremity, but any muscle group can be involved, including the psoas or trunk muscles. Initially, it may not be possible to palpate a discrete abscess because the infection is localized deep within the muscle, but the area has a firm, wooden feel associated with pain and tenderness. In the early stages, ultrasonography or CT scan may be performed to differentiate this entity from a deep venous thrombosis. In more advanced cases, a bulging abscess is usually clinically apparent. Appropriate antibiotics plus extensive surgical incision and drainage are required for appropriate management.

Synergistic Necrotizing Cellulitis

This is simply a necrotizing soft-tissue infection that involves muscle groups in addition to superficial tissues and fascia. The level of involvement depends on the depth and the tissue planes affected by the original operation or pathological process that precedes the infection. Major predisposing causes are perirectal and ischiorectal abscesses. Recognition and treatment are similar to necrotizing fasciitis, but operative exploration reveals its deeper location.

Fournier Gangrene

This variant of necrotizing soft-tissue infection involves the scrotum and penis or vulva and can have an insidious or explosive onset [105, 106]. The mean age of onset is 50 years. Most patients have significant underlying disease, particularly diabetes, but 20% will have no discernible cause. Most patients initially have a perianal or retroperitoneal infection that has spread along fascial planes to the genitalia; a urinary tract infection, most commonly secondary to a urethral stricture, that involves the periurethral glands and extends into the penis and scrotum; or previous trauma to the genital area, providing access of organisms to the subcutaneous tissues.

The infection can begin insidiously with a discrete area of necrosis in the perineum that progresses rapidly over 1–2 days with advancing skin necrosis. At the outset, it tends to cause superficial gangrene, limited to skin and subcutaneous tissue, and extending to the base of the scrotum. The testes, glans penis, and spermatic cord usually are spared, because they have a separate blood supply. The infection may extend to the perineum and the anterior abdominal wall through the fascial planes.

Most cases are caused by mixed aerobic and anaerobic flora. Staphylococci and *Pseudomonas* species are frequently present,

usually in mixed culture, but occasionally, *S. aureus* is the only pathogen. *Pseudomonas* is another common organism in the mixed culture. As with other necrotizing infections, prompt and aggressive surgical exploration and appropriate debridement is necessary to remove all necrotic tissue, sparing the deeper structures when possible (A-III).

Clostridial Myonecrosis

Clostridial gas gangrene (i.e., myonecrosis) is most commonly caused by *C. perfringens*, *C. novyi*, *C. histolyticum*, and *C. septicum*. *C. perfringens* is the most frequent cause of trauma-associated gas gangrene. Increasingly severe pain beginning at the injury site ≤ 24 h after infection is the first reliable symptom. Skin may initially be pale, but it quickly changes to bronze and then to a purplish red. The infected region becomes tense and tender, and bullae filled with reddish-blue fluid appear. Gas in the tissue, detected as crepitus or on the basis of imaging studies, is universally present by this late stage. Signs of systemic toxicity, including tachycardia, fever, and diaphoresis, develop rapidly, followed by shock and multiple organ failure.

In contrast to traumatic gas gangrene, spontaneous gangrene is principally associated with the more aerotolerant *C. septicum* and occurs predominantly in patients with neutropenia and gastrointestinal malignancy. It develops in normal skin in the absence of trauma as a result of hematogenous spread from a colonic lesion, usually cancer. A rather innocuous early lesion may evolve to all of the above signs over the course of 24 h. Frequently, the diagnosis is unsuspected until gas is detected in tissue or systemic signs of toxicity appear. Early surgical inspection and debridement are necessary, and Gram stain of removed tissue shows large, spore-forming gram-positive bacilli.

Both traumatic and spontaneous clostridial gas gangrene are fulminant infections requiring meticulous intensive care, supportive measures, aggressive surgical debridement, and appropriate antibiotics. The role of hyperbaric oxygen treatment remains unclear. Altemeier and Fullen [107] reported a significant reduction in mortality among patients with gas gangrene using penicillin and tetracycline plus aggressive surgery in the absence of hyperbaric oxygen. Treatment of experimental gas gangrene has demonstrated that tetracycline, clindamycin, and chloramphenicol were more effective than penicillin [108, 109] or hyperbaric oxygen treatment [110]. Because 5% of strains of *C. perfringens* are clindamycin resistant, the recommended antibiotic treatment is penicillin plus clindamycin (B-III).

ANIMAL BITES

One-half of all Americans are bitten during their lifetime, usually by a dog. Fortunately, 80% of the wounds are minor, but the remaining 20% that require medical care will account for 1% of all emergency department visits and for 10,000 inpatient

admissions yearly. Most bites are due to dogs or cats, but bites from exotic pets and from feral animals also occur. The predominant pathogens in these wounds are the normal oral flora of the biting animal, along with human skin organisms and occasional secondary invaders (e.g., *S. aureus* and *S. pyogenes*) [111, 112]. There are no published large case series on the therapy of bite wounds, but there are many smaller series and anecdotal reports especially focusing on complications.

Bacteriologic characteristics. Patients who present <8 h after injury seek either wound care or tetanus toxoid, and some are concerned about rabies. Patients who seek medical care after 8–12 h of injury typically have established infection. The wounds may be nonpurulent (30% of dog bites and 42% of cat bites), purulent (58% of dog bites and 39% of cat bites), or abscesses (12% of dog bites and 19% of cat bites). The average wound yields 5 types of bacterial isolates (range, 0–16 types of bacterial isolates), with ~60% yielding mixed aerobic and anaerobic bacteria. *Pasteurella* species are isolated from 50% of dog bite wounds and 75% of cat bite wounds. Staphylococci and streptococci are found in ~40% of bites from both types of animals. *Capnocytophaga canimorsus* (formerly known as DF-2), a fastidious gram-negative rod, can cause bacteremia and fatal sepsis after animal bites, especially in patients with asplenia or underlying hepatic disease. Facultative gram-negative rods are uncommon. *Bacteroides* species, fusobacteria, *Porphyromonas* species, *Prevotella heparinolytica*, propionibacteria, and peptostreptococci are common anaerobes isolated from both dog bite wounds and cat bite wounds [113].

Antimicrobial therapy. Empirical treatment of dog and cat bites is similar (table 6). Although cat bite wounds have little crush injury and less wound trauma than do dog bites, they are often more severe and have a higher proportion of osteomyelitis and septic arthritis. Cat bites have a greater prevalence of anaerobes (65% vs. 50%) and *P. multocida* (75% vs. 50%) than do dog bites. For oral, outpatient therapy, amoxicillin-clavulanate has been studied in a small series [114] and is recommended (B-II). Alternative oral agents include doxycycline, as well as penicillin VK plus dicloxacillin. Other options, including fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin, and gatifloxacin), trimethoprim-sulfamethoxazole, and cefuroxime, may require an additional agent active against anaerobes, such as metronidazole or clindamycin. First-generation cephalosporins, such as cephalexin, penicillinase-resistant penicillins (e.g., dicloxacillin), macrolides (e.g., erythromycin), and clindamycin, all have poor in vitro activity against *P. multocida* and should be avoided (D-III).

Intravenous options include the β -lactam/ β -lactamase combinations (such as ampicillin sulbactam), piperacillin/tazobactam, second-generation cephalosporins (such as cefoxitin), and carbapenems (such as ertapenem, imipenem, and meropenem) (B-II). Second-generation and third-generation cephalosporins,

such as cefuroxime, ceftriaxone, and cefotaxime, may be used but may require the addition of an antianaerobic agent.

Penicillin-allergic pregnant women constitute a special population, because tetracyclines, sulfa compounds (during late pregnancy), and metronidazole are contraindicated. Similarly, the selection of an antimicrobial for penicillin-allergic children is problematic when tetracyclines and fluoroquinolones are contraindicated. In these situations, macrolides (e.g., azithromycin 250–500 mg every day or telithromycin 400 mg, 2 tablets by mouth every day) are occasionally used. However, these patients should be observed closely and the potential increased risk of failure noted.

The duration of therapy varies by the severity of the injury/infection. Cellulitis and abscess often respond to 5–10 days of therapy. The therapy for early presenting, noninfected wounds remains controversial. Wounds that are moderate to severe, have associated crush injury, have associated edema (either pre-existing or subsequent), that are on the hands or in proximity to a bone or a joint, or that are in compromised hosts should receive 3–5 days of “prophylactic” antimicrobial therapy. These wounds are often colonized with potential pathogens (85% of cases), and it is difficult to determine whether the wound will become infected.

Complications. Infectious complications of bite wounds include septic arthritis, osteomyelitis, subcutaneous abscess formation, tendonitis, and, rarely, bacteremia. Pain disproportionate to the severity of injury but located near a bone or joint should suggest periosteal penetration. Hand wounds are often more serious than wounds to fleshy parts of the body. These wound complications will necessitate prolonged therapy, such as 4–6-week courses for osteomyelitis and 3–4-week courses for synovitis. Noninfectious complications include nerve or tendon injury or severance, compartment syndromes, postinfectious and traumatic arthritis, fracture, and bleeding.

Adjunctive therapeutic measures are often as important as antimicrobial therapy. Wounds should be cleansed with sterile normal saline (no need for iodine- or antibiotic-containing solutions) and superficial debris removed. Deeper debridement is usually unnecessary, but, if performed, should be done very cautiously to avoid enlarging the wound and impairing skin closure. Infected wounds should not be closed. Suturing wounds early (<8 h after injury) is controversial, and there are no studies to delineate guidelines; however, approximation of the margins by Steri-Strips (3M Health Care) and subsequent closure by either delayed primary or secondary intent seem prudent. Wounds on the face seem to be an exception and can be closed primarily if seen by a plastic surgeon, provided there has been meticulous wound care, copious irrigation, and administration of prophylactic antibiotics. During the first few days after injury, elevation of the injured body part, especially if swollen, accelerates healing. This should be accomplished

using a passive method (a sling for outpatients or a tubular stockinet and an intravenous pole for inpatients).

Outpatients should be followed up within 24 h either by phone or during an office visit. If infection progresses despite good antimicrobial and ancillary therapy, hospitalization should be considered. On occasion, a single initial dose of a parenteral antimicrobial may be administered before starting oral therapy. Clinicians should insure that tetanus prophylaxis status is current. If it is outdated or if the status is unknown, then a dose of tetanus toxoid (0.5 mL intramuscularly) should be administered. Rabies prophylaxis should be considered for all feral and wild animal bites and in geographic areas where there is a high prevalence of rabies. The local department of health should be consulted about the risks and benefits of rabies prophylaxis (administration on day 0 of rabies immunoglobulin, followed by rabies human diploid cell vaccination at a different site). Only anecdotal literature exists regarding the bacteriologic characteristics and therapy of exotic or wild animal bites, but the same general principles should apply.

HUMAN BITES

Human bite wounds often result from aggressive behavior and are frequently more serious than animal bites. Wounds may be either occlusive injuries, in which the teeth actually bite the body part, or clenched-fist injuries, which occur when the fist of one person strikes the teeth of another. Between 10% and 20% of occlusive wounds occur during sexual interactions. Bite wounds in children may be associated with sports-related activity (look for imbedded teeth) but should also alert the clinician to possible child abuse.

Bacteriologic characteristics. The bacteriologic characteristics of these wounds reflect the normal oral flora of the biter, with streptococci (especially viridans streptococci) in 80% of wounds, as well as staphylococci, *Haemophilus* species, and *Eikenella corrodens* as prominent aerobic pathogens [112, 115]. Other gram-negative rods are infrequent. Anaerobes, including *Fusobacterium nucleatum* and other *Fusobacterium* species, peptostreptococci, *Prevotella* species, and *Porphyromonas* species, are present in >60% of cases, but usually in mixed culture. *Bacteroides fragilis* is rarely present. Many of the anaerobes produce β -lactamases, making them resistant to penicillin and first-generation cephalosporins. Human bites also have the potential to transmit various viral diseases, such as herpes, hepatitis B and C, and HIV infection [116–120].

Therapy. Evaluation and treatment should follow the general principles outlined for animal bites, with irrigation and topical wound cleansing, except that prophylactic antimicrobials should be given as early as possible to all patients regardless of the appearance of the wound (table 6). An expert in hand care should evaluate clenched-fist injuries for penetration into the synovium, joint capsule, and the bone (B-III). These

wounds, although often quite small, may extend deeply into the hand tissues, and relaxation of the fist may carry organisms into the deep compartments and potential spaces of the hand. Exploration under tourniquet control may be necessary. Clenched-fist injuries often require hospitalization and intravenous antimicrobial therapy with agents such as cefoxitin (1 g intravenously every 6–8 h), ampicillin-sulbactam (1.5–3 g intravenously every 6 h), ertapenem (1 g intravenously every 24 h), or some combination that covers *S. aureus*, *Haemophilus* species, *E. corrodens*, and β -lactamase-producing anaerobes (B-III). *E. corrodens* is usually resistant to first-generation cephalosporins (e.g., cefazolin and cephalexin), macrolides (e.g., erythromycin), clindamycin, and aminoglycosides, and these agents should be avoided as monotherapy. In the type 1 β -lactam-allergic patient, fluoroquinolones (e.g., moxifloxacin and gatifloxacin) plus clindamycin, or trimethoprim-sulfamethoxazole plus metronidazole may be useful. Ancillary measures include administration of tetanus toxoid as indicated. The duration of therapy is typically 4 weeks for septic arthritis and 6 weeks for osteomyelitis.

Complications. Complications are frequent and include tendon and nerve damage, fractures, septic arthritis, and osteomyelitis. Splinting of the hand in a position of function is often required, as is subsequent physical therapy. Residual joint stiffness is common after clenched fist injury and may affect function.

SOFT-TISSUE INFECTIONS FOLLOWING ANIMAL CONTACT

Anthrax. One of several clinical manifestations of anthrax is a cutaneous lesion. After an incubation period of 1–12 days, pruritus begins at the entry site, followed by a papule, development of vesicles on top of the papule, and, finally, a painless ulcer with a black scab. This eschar generally separates and sloughs after 12–14 days. Swelling surrounding the lesion can be minor or severe (i.e., malignant edema). Mild-to-moderate fever, headaches, and malaise often accompany the illness. Regional lymphadenopathy is common, but pus in the lesion is absent unless a secondary infection occurs. WBC counts are generally normal, but mild leukocytosis can occur. Blood culture results are almost always negative. Cultures of untreated lesions, depending on the stage of evolution, have positive results >80% of the time. Methods of specimen collection for culture depend on the type of lesion. With vesicles, the blister should be unroofed and 2 dry swabs soaked in the fluid. At a later stage, 2 moist swabs should be rotated in the ulcer base or beneath the eschar's edge. Patients who have previously received antimicrobials or who have negative results of tests but still have suspected cutaneous anthrax should have a punch biopsy specimen obtained that can be submitted for special studies, such as immunohistochemical staining and/or PCR.

Table 6. Recommended therapy for infections following animal or human bites.

| Antimicrobial agent, by type of bite | Route of drug administration | | Comment |
|---|---------------------------------------|-----------------------|---|
| | Oral | Intravenous | |
| Animal bite | | | |
| Amoxicillin/clavulanate | 500/875 mg twice per day ^a | ... | Some gram-negative rods are resistant; misses MRSA |
| Ampicillin-sulbactam | ... | 1.5–3.0 g every 6–8 h | Some gram-negative rods are resistant; misses MRSA |
| Piperacillin/tazobactam | ... | 3.37 g every 6–8 h | Misses MRSA |
| Carbapenem | | | |
| Ertapenem | ... | 1 g every day | |
| Imipenem | ... | 1 g every 6–8 h | |
| Meropenem | ... | 1 g every 8 h | |
| Doxycycline | 100 mg twice per day | ... | Excellent activity against <i>Pasteurella multocida</i> ; some streptococci are resistant |
| Penicillin | 500 mg 4 times per day | ... | |
| plus | | | |
| dicloxacillin | 500 mg 4 times per day | ... | |
| TMP-SMZ | 160–800 mg twice per day | ... | Good activity against aerobes; poor activity against anaerobes |
| Metronidazole | 250–500 mg 4 times per day | ... | Good activity against anaerobes; no activity against aerobes |
| Clindamycin | 300 mg 3 times per day | ... | Good activity against staphylococci, streptococci and anaerobes; misses <i>P. multocida</i> |
| First-generation cephalosporin | | | Good activity against staphylococci and streptococci; misses <i>P. multocida</i> and anaerobes |
| Cephalexin | 500 mg 3 times per day | ... | |
| Cefazolin | ... | 1 g every 8 h | |
| Second-generation cephalosporin | | | Good activity against <i>P. multocida</i> ; misses anaerobes |
| Cefuroxime | 500 mg twice per day | 1 g every day | |
| Cefoxitin | ... | 1 g every 6–8 h | |
| Third-generation cephalosporin | | | |
| Ceftriaxone | ... | 1 g every 12 h | |
| Cefotaxime | ... | 2 g every 6 h | |
| Fluoroquinolones | | | Good activity against <i>P. multocida</i> ; misses MRSA and some anaerobes |
| Ciprofloxacin | 500–750 mg twice per day | 400 mg every 12 h | |
| Gatifloxacin | 400 mg every day | ... | |
| Moxifloxacin | 400 mg every day | 400 mg every day | |
| Human bite | | | |
| Amoxicillin/clavulanate | 500 mg every 8 h ^a | ... | Some gram-negative rods are resistant; misses MRSA |
| Ampicillin/sulbactam | ... | 1.5– 3.0 g every 6 h | Some gram-negative rods are resistant; misses MRSA |
| Carbapenem | | | Misses MRSA |
| Ertapenem | ... | 1 g every day | |
| Imipenem | ... | 1 g every day | |
| Meropenem | ... | 1 g every day | |
| Doxycycline | 100 mg twice per day | ... | Good activity against <i>Eikenella</i> species, staphylococci, and anaerobes; some streptococci are resistant |

(continued)

Table 6. (Continued.)

| Antimicrobial agent, by type of bite | Route of drug administration | | Comment |
|---|------------------------------|-------------------|--|
| | Oral | Intravenous | |
| TMP-SMZ | 160–800 mg twice per day | ... | Good activity against aerobes; poor activity against anaerobes |
| Metronidazole | 250–500 mg 4 times per day | ... | Good activity against anaerobes; poor activity against aerobes |
| Clindamycin | 300 mg 3 times per day | ... | Good activity against staphylococci, streptococci, and anaerobes; misses <i>Eikenella corrodens</i> |
| Cephalosporin | | | Good activity against staphylococci and streptococci; misses <i>E. corrodens</i> and gram-negative anaerobes |
| Cephalexin | 500 mg 4 times per day | ... | |
| Cefazolin | ... | 1 g every 8 h | |
| Fluoroquinolone | | | Good activity against <i>E. corrodens</i> ; misses MRSA and some anaerobes |
| Ciprofloxacin | 500–750 mg twice per day | 400 mg every 12 h | |
| Gatifloxacin | 400 mg every day | 400 mg every day | |
| Moxifloxacin | 400 mg every day | 400 mg every day | |

NOTE. As a rule, the use of fluoroquinolones is contraindicated by the US Food and Drug Administration for children and adolescents <18 years of age. It should also be noted that tetracyclines are rarely used in children younger than 8 years of age. Alternatives should be strongly considered for these two antibiotics [6]. MRSA, methicillin-resistant *Staphylococcus aureus*. TMP-SMZ, trimethoprim-sulfamethoxazole.

^a Should be given with food.

When obtaining specimens, lesions should not be squeezed to produce material for culture. Additional diagnostic methods include serologic and skin tests.

No randomized, controlled trials of therapy of cutaneous anthrax exist. Most published data indicate that penicillin is effective therapy (B-III) (table 3) and will “sterilize” most lesions between a few hours to 3 days but does not accelerate healing. Its value seems to be primarily in reducing mortality from as high as 20% to 0%. On the basis of even less evidence, tetracyclines, chloramphenicol, and erythromycin also appear to be effective.

Suggested antimicrobials and dosages derive from 3 publications (table 3) [121–123]. The optimal duration of treatment is uncertain, but 5–9 days appears to be adequate. Sixty days of treatment is recommended when infection is associated with bioterrorism, because concomitant inhalation may have occurred. Until results of susceptibility tests are available, ciprofloxacin is rational empirical therapy (B-III), especially with the possibility of genetically altered *B. anthracis*. Other fluoroquinolones, such as levofloxacin, gatifloxacin, or moxifloxacin, are also likely to be effective. Initiation of intravenous versus oral therapy depends on the severity of the illness, particularly the degree of edema.

Some have suggested systemic corticosteroid therapy for patients who develop malignant edema, especially of the head and neck, but studies supporting this recommendation are lacking. Airway compromise requiring intubation or tracheostomy may occur with malignant edema.

Cat-scratch disease and bacillary angiomatosis. *Bartonella henselae* causes most cases of cat-scratch disease in immunocompetent hosts. Bacillary angiomatosis, seen in immunocompromised patients, especially with AIDS, can occur from either *B. henselae* or *Bartonella quintana*. In classic cat-scratch disease, a papule or pustule develops 3–30 days after a scratch or a bite. Regional adenopathy occurs ~3 weeks after inoculation in nodes that drain the infected area. Extranodal disease (such as that found in the CNS, liver, spleen, bone, and lung) develops in ≤2% of cases. In ~10% of cases, the nodes suppurate. The disease course varies, but lymphadenopathy generally resolves within 1–6 months.

Cutaneous bacillary angiomatosis has 2 clinical appearances. The dermal form is a red papule that varies in size from 1 millimeter to several centimeters, and the number of lesions may vary from 1 to >1000. The second form is a painful subcutaneous nodule with overlying skin having a normal or dusky hue.

Definitive confirmation of *Bartonella* infections may be difficult, because these fastidious organisms infrequently grow from pus or nodal tissue. Serologic testing supports the diagnosis. However, cross-reactivity occurs between *B. henselae* and *B. quintana*, as well as with a few other organisms. PCR, although mainly a research tool, is also a diagnostic option. Routine histologic examination of a node, coupled with the clinical findings, may strongly suggest the diagnosis. Histologic examination in conjunction with a Wharthin-Starry silver stain is helpful but does not differentiate the species of *Bartonella*.

Aspiration of fluctuant nodes may exclude other causes of purulent lymphadenopathy and sometimes is appropriate to relieve pain.

Treatment of cat-scratch disease with antimicrobial agents has had variable, but rarely dramatic, results. A single, double-blind, placebo-controlled study involved 29 patients, 14 of whom received azithromycin [124]. The lymph node size had regressed 30 days after treatment more often in the azithromycin-treated patients ($P = .02$). If antimicrobial therapy is used, patients weighing >45.5 kg (>100 lbs) should receive 500 mg of azithromycin orally on day 1, followed by 250 mg once daily for 4 additional days (A-I). Those weighing less than the weight listed above should receive 10 mg/kg orally on day 1, followed by 5 mg/kg on days 2–5 [124]. Cutaneous bacillary angiomatosis therapy has not been systematically examined. On the basis of results of case reports and small series, either erythromycin (500 mg 4 times per day) or doxycycline (100 mg twice per day) appear to be effective (B-III). The duration of initial therapy, although not standardized, should be at least 4 weeks. With relapses, retreatment with prolonged therapy (lasting several months) should be entertained until immunocompetence returns. Other antimicrobials with some efficacy are rifampin, trimethoprim-sulfamethoxazole, and ciprofloxacin [125].

Erysipeloid. Erysipeloid is a cutaneous infection caused by the thin, pleomorphic, non-spore-forming gram-positive rod *E. rhusiopathiae*. It is a zoonosis seen in persons who handle fish, marine animals, swine, or poultry. Between 1 and 7 days after exposure, a red maculopapular lesion develops, usually on the fingers or hands. Erythema spreads centrifugally with central clearing. A blue ring with a peripheral red halo may appear, giving the lesion a target appearance. Regional lymphangitis and/or lymphadenopathy occurs in about one-third of cases. A severe, generalized cutaneous infection also occurs. However, systemic symptoms and leukocytosis are unusual. Culture of a lesion aspirate and/or biopsy specimen establishes the diagnosis, but the results of blood cultures are rarely positive. Untreated erysipeloid resolves during a period of 3–4 weeks, but treatment probably hastens healing and perhaps reduces systemic complications. Most of the literature concerning therapy relates to endocarditis, in which high-dose penicillin is generally used. On the basis of in vitro susceptibilities and anecdotal statements, penicillin is appropriate (B-III), although the optimum duration of therapy is unknown. For cutaneous infection, penicillin (500 mg orally 4 times per day) or amoxicillin (500 mg 3 times per day) for 7–10 days seems to be rational. For patients who are intolerant of penicillins, treatment with cephalosporins, clindamycin, or fluoroquinolones should be effective. *E. rhusiopathiae* is resistant to vancomycin, teicoplanin, and daptomycin [125, 126].

Glanders. Glanders, caused by the aerobic gram-negative

rod *Burkholderia mallei*, is mainly a disease of solipeds (e.g., horses and mules). Humans become accidental hosts either by inhalation or skin contact. Although other organs may be involved, pustular skin lesions and lymphadenopathy with suppurative nodes can be a prominent feature. Almost all glanders infections preceded the antibiotic era. Results of in vitro susceptibility tests suggest that ceftazidime, gentamicin, imipenem, doxycycline, and ciprofloxacin should be effective. A recent laboratory-acquired case was successfully treated with imipenem and doxycycline for 2 weeks, followed by azithromycin and doxycycline for an additional 6 months [127].

Bubonic plague. Plague results from infection with *Y. pestis*, a facultative, anaerobic gram-negative coccobacillus. It primarily affects rodents, being maintained in nature by several species of fleas that feed on them. Three plague syndromes occur in humans: septicemic, pneumonic, and bubonic. Bubonic plague, the most common and classic form, develops when humans are bitten by infected fleas or have a breach in the skin when handling infected animals. Domestic cat scratches or bites may also transmit bubonic plague. Patients usually develop fever, headache, chills, and tender regional lymphadenopathy 2–6 days after contact with the organism. A skin lesion at the portal of entry is sometimes present. Patients with bubonic plague may develop septicemia and secondary plague pneumonia, the latter permitting person-to-person transmission. Diagnosis can be made by blood cultures and by aspirating lymph nodes for staining and culture. PCR and other more sophisticated tests are generally available only at reference laboratories. Results of serologic tests may provide retrospective confirmation.

No controlled comparative trials of therapy for plague exist. Streptomycin has been the drug of choice (B-III), although tetracycline and chloramphenicol are also considered to be appropriate therapy (table 7). Although there have been no recent reports of treatment of any sizable numbers of cases of plague, studies from the Vietnam War period showed that most patients actually received streptomycin plus either tetracycline or chloramphenicol. Some patients have been successfully treated with kanamycin. Gentamicin has been suggested as a substitute for streptomycin, but its use in humans has been limited. On the basis of in vitro susceptibilities and murine models, fluoroquinolones are another option. A multidrug-resistant strain of *Y. pestis* has been isolated in Madagascar, and it is suspected that an antimicrobial-resistant strain of the plague bacillus has been developed for biologic warfare. Unless introduced into the rodent population, however, *Y. pestis* as a biowarfare agent is much more likely to be used as an aerosol, thus producing pneumonic plague rather than bubonic plague. Ciprofloxacin has been suggested as a drug for both treatment and prevention of plague due to biowarfare agents, despite a lack of documented efficacy in humans. The optimal duration for treating

Table 7. Therapy for bubonic plague.

| Drug | Dosage | |
|----------------------------|---|---|
| | Adults (including pregnant women) | Children ^a |
| Streptomycin ^b | 1 g im twice per day | 30 mg/kg im daily in 2 divided doses |
| Gentamicin ^b | 2 mg/kg loading dose, followed by 1.7 mg/kg/day in 3 divided doses iv | 2 mg/kg every 8 h iv |
| Tetracycline ^c | 500 mg po every 6 h | ... |
| Chloramphenicol | 25 mg/kg iv every 6 h (not to exceed 6 g total dose daily) | 25 mg/kg iv every 6 h (not to exceed 6 g total dose daily) |
| Doxycycline ^c | 100 mg iv or po twice daily | Persons who weigh >45 kg: 100 mg iv or po twice daily; persons who weigh ≤45 kg: 2.2 mg/kg iv or po twice daily |
| Ciprofloxacin ^c | 500 mg po twice daily or 400 mg iv twice daily | 20 mg/kg po twice daily or 15 mg/kg iv twice daily |

NOTE. Agents of bioterrorism may be genetically altered for antimicrobial resistance. im, intramuscularly; iv, intravenously; po, orally.

^a Not appropriate for neonates.

^b Aminoglycoside dosages need adjustment according to renal function.

^c Doxycycline, tetracycline, and ciprofloxacin should be used only under exceptional circumstances in children <8 years of age or during pregnancy.

bubonic plague is unknown, but 10–14 days is probably adequate. In view of the forgoing, the recommendations in reviews by Perry and Fetherston [128] and by Inglesby et al. [129] seem to be rational (table 7). Patients with bubonic plague should be placed in respiratory isolation until completion of 48 h of effective drug therapy, because some develop secondary pneumonic plague.

Tularemia—ulceroglandular or glandular. *F. tularensis*, although hardy and persistent in nature, is a fastidious, aerobic, gram-negative coccobacillus. Illness can often be categorized into several fairly distinct syndromes—ulceroglandular, glandular, typhoidal, pneumonic, oculoglandular, or oropharyngeal. The glandular varieties are generally acquired by handling infected animals, by tick bites, and sometimes by animal bites, especially from cats. Biting flies occasionally transmit the illness in the United States, whereas mosquitoes are common vectors in Europe. After an incubation period of 3–10 days, the patient typically develops a skin lesion (an ulcer or an eschar) at the entry site of the organism, along with tender regional adenopathy in the lymph nodes—thus the term “ulceroglandular.” In some patients, the skin lesion is inconspicuous or healed by the time that they seek medical care, resulting in “glandular” tularemia. The illness is often associated with substantial fever, chills, headache, and malaise.

Confirmation of the diagnosis is usually accomplished by means of serologic testing. Results of routine cultures are often negative unless cysteine-supplemented media are used. Unsuspected growth of *Francisella* species can cause laboratory-acquired disease. PCR shows considerable promise for diagnosis.

No prospective controlled or randomized trials of therapy for tularemia have been performed, nor has the optimal duration of treatment been established, but many patients will require initiation of treatment before confirmation of the diagnosis. Streptomycin has been considered to be the drug of

choice for tularemia for several decades (B-III). A 1994 review found 294 cases treated with streptomycin but only 20, 43, and 36 patients treated with tetracycline, chloramphenicol, and gentamicin, respectively [130]. Since then, a few patients have been received fluoroquinolones. *Francisella* species are resistant to most β -lactam antibiotics. Even with favorable in vitro susceptibilities, failure rates with ceftriaxone have been high. One patient has responded to imipenem, and 2 patients have responded to erythromycin. When static drugs such as tetracyclines or chloramphenicol are used, relapses may be more common, but often the patients have received brief therapy (duration, <7 to 10 days).

Acutely ill adults or children should receive an aminoglycoside, preferably streptomycin or possibly gentamicin. For adults, the regimen for streptomycin is 30 mg/kg per day in 2 divided doses (<2 g daily) or gentamicin 3–5 mg/kg per day in 3 divided doses. For children, streptomycin should be administered at 30 mg/kg per day in 2 divided doses and gentamicin at 6 mg/kg per day in 3 divided doses [130]. Treatment duration of 7–10 days is appropriate, with dosages of aminoglycosides adjusted according to renal function. Although no data exist, treatment with a parenteral agent until the acute illness is controlled, followed by an oral agent, seems to be rational.

In mild-to-moderate disease, oral tetracycline (500 mg 4 times per day) or doxycycline (100 mg twice per day) is appropriate. Chloramphenicol (2–3 g daily in 4 divided doses) has been used in adults. Oral chloramphenicol is no longer distributed in the United States, and the rare, but serious adverse effect—bone marrow aplasia—makes it an undesirable agent. A few cases have been treated with fluoroquinolones, with mixed results [131–133]. Oral levofloxacin (500 mg daily) or ciprofloxacin (750 mg twice per day) in adults may be rea-

sonable for mild to moderate illness. With oral regimens, patients should receive at least 14 days of therapy.

SURGICAL SITE INFECTIONS (SSIs)

Infections of surgical wounds are the most common adverse events affecting hospitalized patients who have undergone surgery [134]. Data from the National Nosocomial Infection Surveillance System show an average SSI incidence of 2.6%, accounting for 38% of nosocomial infections in surgical patients [135]. The frequency of SSI is clearly related to the category of operation, with clean and low-risk operations (as defined by the National Nosocomial Infection Surveillance System classification) having the lowest rate of infection and contaminated and high-risk operations having greater infection rates [136]. Very few sources of objective evidence compare treatments for SSI.

SSIs are divided into the categories of superficial incisional SSI, deep incisional SSI, and organ/space SSI [135]. Superficial incisional SSIs involve only the subcutaneous space, between the skin and underlying muscular fascia, occur within 30 days of the index operation, and are documented with at least 1 of the following findings: (1) purulent incisional drainage; (2) positive results of culture of aseptically obtained fluid or tissue from the superficial wound; (3) local signs and symptoms of pain or tenderness, swelling, and erythema, with the incision opened by the surgeon (unless culture results are negative); or (4) diagnosis of SSI by the attending surgeon or physician.

A deep incisional infection involves the deep layers of soft tissue (e.g., fascia and muscle) in the incision and occurs within 30 days after the operation or within 1 year after the operation if a prosthesis was inserted and has the same findings as described for a superficial incisional SSI.

An organ/space SSI has the same time constraints and evidence for infection as a deep incisional SSI and involves any part of the anatomy (organs or spaces) other than the incision opened during the operation [135]. Superficial and deep incisional SSIs are skin and soft-tissue infections and will be discussed in this guideline. Organ/space SSIs are usually dealt with separately as infections related to the relevant organ and space. Any deep SSI that does not resolve in the expected manner after treatment should be investigated as a possible superficial manifestation of a deeper organ/space infection.

In diagnosing SSIs, the physical appearance of the incision probably provides the most reliable information. Local signs of pain, swelling, erythema, and purulent drainage are usually present. In morbidly obese patients or in patients with deep, multilayer wounds (such as wounds following thoracotomy), the external signs of SSIs may be very late but always appear. Although many patients with SSIs will have fever, it usually does not occur immediately after operation, and in fact, most postoperative fevers are not associated with SSI [137]. Flat,

erythematous changes can occur around or near a surgical incision during the first week without swelling or wound drainage. Most resolve without any treatment, including antibiotics. The cause is unknown but may relate to tape sensitivity or to other local tissue insult not involving bacteria. Numerous experimental studies and clinical trials examining the prevention of SSIs demonstrate that antibiotic therapy that is begun immediately after surgery or that is continued for long periods after the procedure does not prevent or cure this inflammation or infection [138–143]. Therefore, the suspicion of possible SSI does not justify use of antibiotics without a definitive diagnosis and the initiation of other therapeutic measures, such as opening the wound (B-III) (figure 1).

Most SSIs have no clinical manifestations for at least 5 days after the operation, and many may not become apparent for up to 2 weeks. Later infections are less likely, but surveillance standards mandate a follow-up duration of 30 days. Rarely does any bacterial pathogen cause fever and clinical evidence of soft-tissue infection within the first 48 h after an operation or injury. Infections that do occur in this time frame are almost always due to *S. pyogenes* or *Clostridium* species. Accordingly, fever or systemic signs during the first several days after surgery should be followed by direct examination of the wound to rule out signs suggestive of streptococcal or clostridial infection but should not otherwise cause further manipulation of the wound. Patients with an early infection due to streptococci or clostridia have wound drainage with the responsible organisms present on Gram stain. WBCs may not be evident in most clostridial and some early streptococcal infections. Another rare cause of early fever and systemic signs after operation is toxic shock syndrome due to staphylococcal wound infection [144, 145]. In these cases, the wound is often deceptively benign in appearance. Erythroderma occurs early but not immediately, and desquamation occurs late. Fever, hypotension, abnormal hepatic and renal blood findings, and diarrhea may be early findings. Treatment is to open the incision, obtain and culture a wound specimen, and begin antistaphylococcal treatment.

The primary, and most important, therapy for SSI is to open the incision, evacuate the infected material, and continue dressing changes until the wound heals by secondary intention.

Although patients commonly receive antibiotics when SSI is first diagnosed, there is little or no evidence supporting this practice. Studies of subcutaneous abscesses found no benefit for antibiotic therapy when combined with drainage [24, 33]. The single published trial of antibiotic administration for SSIs found no clinical benefit associated with this treatment [146]. Most textbooks of surgery, infectious diseases, or even surgical infectious diseases extensively discuss the epidemiologic characteristics, prevention, and surveillance of SSIs but not their treatment [147–153]. Two articles contain simple, unrefer-

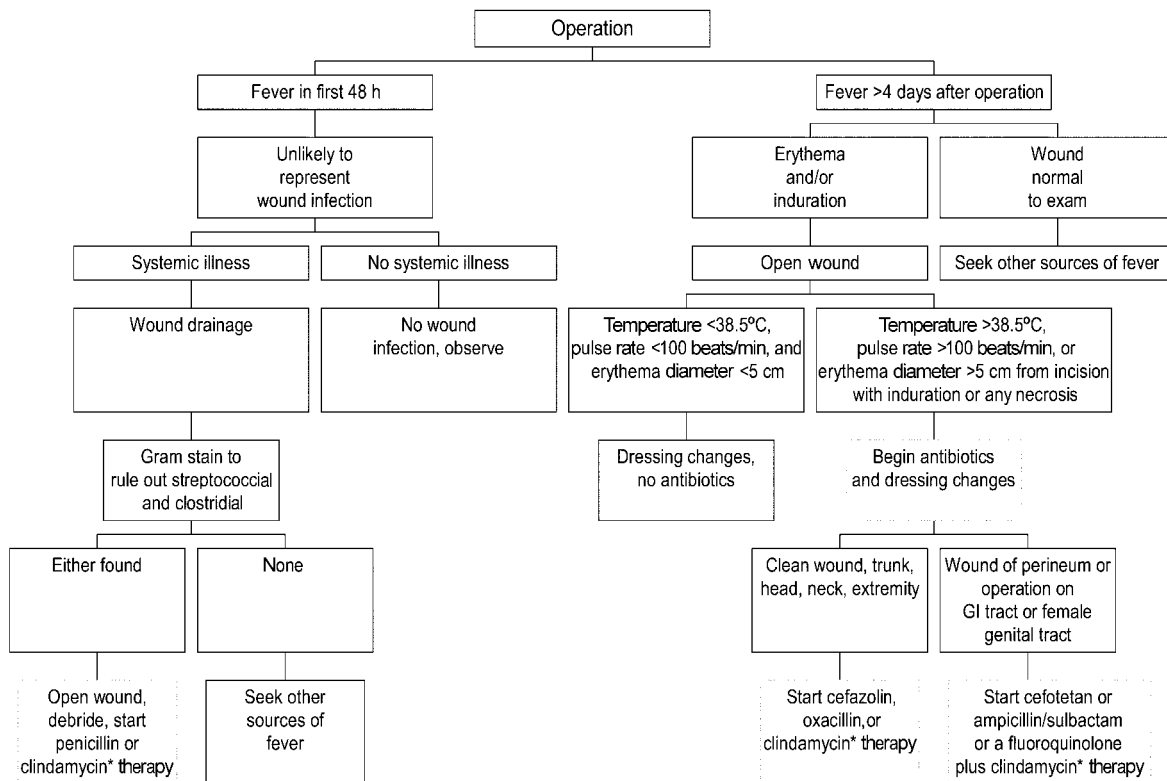


Figure 1. Algorithm for the management and treatment of surgical site infections. *For patients with type 1 (anaphylaxis or hives) allergy to β -lactam antibiotics. Where the rate of infection with methicillin-resistant *Staphylococcus aureus* infection is high, consider vancomycin, daptomycin, or linezolid, pending results of culture and susceptibility tests. Adapted and modified with permission from [154]. GI, gastrointestinal.

enced, recommendations to open an infected wound without using antibiotics [154, 155].

A common practice, endorsed by expert opinion, is to open all infected wounds (B-III). If there is minimal surrounding evidence of invasive infection (<5 cm of erythema and induration), and if the patient has minimal systemic signs of infection (a temperature of <38.5°C and a pulse rate of <100 beats/min), antibiotics are unnecessary. Because incision and drainage of superficial abscesses rarely causes bacteremia [156], antibiotics are not needed. For patients with a temperature of >38.5°C or a pulse rate of >100 beats/min, a short course of antibiotics, usually for a duration of 24–48 h, may be indicated. The antibiotic choice is usually empirical but can be supported by findings of Gram stain and results of culture of the wound contents. SSIs that occur after an operation on the intestinal tract or female genitalia have a high probability of having a mixed gram-positive and gram-negative flora with both facultative and anaerobic organisms. If such an infection is being treated with empirical antibiotics, any antibiotic considered to be appropriate for treatment of intra-abdominal infection is reasonable (table 4). If the operation was a clean procedure that did not enter the intestinal or genital tracts, *S. aureus* (including MRSA) and streptococcal species are the most com-

mon organisms. Because incisions in the axilla have a significant recovery of gram-negative organisms and incisions in the perineum have a higher incidence of gram-negative organisms and anaerobes [24, 26, 157], antibiotic choices should be made accordingly (table 4). Figure 1 presents a schematic algorithm to approach patients with suspected SSI [154] and includes specific antibiotic recommendations [158].

INFECTIONS IN THE IMMUNE COMPROMISED HOST

Immunocompromised patients, by definition, are at increased risk of infection and have a decreased ability to control local infection [159–161]. Skin and soft-tissue infections are common, and because they are caused by a wide range of pathogens and are often part of a widely disseminated infection, they frequently pose a difficult clinical problem [162, 163]. Infection prevention in immunocompromised patients is important and demands careful attention to measures that protect the skin from unnecessary trauma, maceration, or alterations in the normal microbial flora. When infections do develop, it is critical to establish a specific etiologic diagnosis, because many are nosocomial and are caused by pathogens with increased anti-

microbial resistance. Skin lesions, no matter how small or innocuous in appearance, should be carefully evaluated, and the clinician must remember that their gross appearance is frequently altered by the decreased inflammatory response. Thus, the initial clinical impressions must be supplemented with a systematic approach for diagnosis and treatment [164, 165].

After considering the important patient-specific factors concerning the patient's immune compromised status (e.g., neutropenia or neutrophil defects, cellular immune defect, and iatrogenic procedures), the gross morphologic characteristics of the skin lesion(s) should be characterized, the extent of the infection determined (e.g., localized vs. disseminated), and appropriate diagnostic tests undertaken to identify the infecting pathogen. Finally, antimicrobial therapy should be initiated, on the basis of the important clinical parameters identified and the most likely offending pathogens [164, 165]. Although blood cultures or tests for detection of antigen in blood or vesicular fluid may be helpful, the most specific method is aspiration or biopsy of the lesion to obtain material for histological and microbiological evaluation. Analysis of lesion biopsy specimens yields positive results for only 20% of otherwise healthy patients with focal skin lesions [57]. Similar prospective studies involving immunocompromised patients have not been performed. Consequently, most clinicians who treat immunocompromised patients combine blood cultures, tests for antigen detection, and radiographic imaging with analysis of a biopsy specimen obtained from the abnormal skin lesion to optimize recovery of the offending pathogen and to direct pathogen-specific antimicrobial therapy and local surgical management.

Predisposition to Infection: Neutropenia

Patients with neutropenia are predisposed to infection because of insufficient circulating neutrophils, lack of adequate myeloid marrow reserve, or congenital or acquired defects in neutrophil function [159–163, 165]. Neutropenia is frequently associated with mucosal or integumentary barrier disruption, and the indigenous colonizing flora are responsible for most infections. More than 20% of patients with chemotherapy-induced neutropenia develop skin and soft-tissue infections, many of which are due to hematogenous dissemination from other sites, such as the sinuses, lungs, and the alimentary tract [162, 163, 166]. Important pathogens for neutropenic patients can be separated into organisms most likely to cause an “initial infection” (characterized by <7 days of fever and neutropenia) and those more likely to cause a “subsequent infection” (with an onset after 7 days of neutropenia) [159, 167]. Pathogens causing initial infections are usually bacteria, including both gram-negative and gram-positive organisms. Pathogens causing subsequent infections are usually antibiotic-resistant bacteria, yeast, or fungi (table 8).

Initial Infection in Neutropenic Patients

Historically, the primary gram-negative pathogens have been *E. coli*, *Klebsiella* species, and *P. aeruginosa*, but there is wide variability in the pathogens isolated in different treatment centers [159, 160, 164, 165]. The relative incidence of gram-negative bacilli as causes of initial infections has decreased significantly during the past 2 decades, but they remain important pathogens for patients with profound neutropenia (<100 polymorphonuclear leukocytes/ μ L) with a prolonged duration (7–10 days) or for patients who have not received antibacterial prophylaxis during their period of neutropenia [168]. Dermatologic manifestations of gram-negative skin and soft-tissue infections include erythematous maculopapular lesions, focal or progressive cellulitis, cutaneous nodules [167], and ecthyma gangrenosum. Ecthyma gangrenosum begins as painless, erythematous, macules that rapidly become painful and necrotic during a 12–24-h period. They may be discrete or multiple; are found preferentially in the groin, axilla, or trunk; and can increase in size from 1 cm to >10 cm in <24 h. Ecthyma gangrenosum is a cutaneous vasculitis caused by bacterial invasion of the media and adventitia of the vessel wall. Progression of the lesion leads to dermal necrosis, and bacteria are often visible during microscopic analysis of biopsy specimens. Ecthyma gangrenosum has classically been reported to occur with *P. aeruginosa* infections, but similar lesions can occur with disseminated infections caused by other *Pseudomonas* species, *Aeromonas* species, *Serratia* species, *S. aureus*, *Stenotrophomonas maltophilia*, *Candida* species, and fungi, including *Aspergillus*, *Mucor*, and *Fusarium* species [166].

The increased use of antimicrobial prophylaxis with fluoroquinolones or trimethoprim-sulfamethoxazole and the frequent reliance on indwelling vascular access devices have resulted in gram-positive organisms being the most frequently isolated pathogens in initial infections [169]. These organisms, in order of decreasing prevalence, include coagulase-negative staphylococci, viridans streptococci, enterococci, *S. aureus*, *Corynebacterium* species, *Clostridium* species, and *Bacillus* species and often represent part of the patient's normal skin flora. Soft-tissue infections due to these pathogens usually begin as a focal area of erythematous cutaneous tenderness, a macular or maculopapular eruption, or as cellulitis. The most frequent infection sites are the groin, axilla, areas of cutaneous disruption (e.g., vascular catheter or bone marrow aspiration sites), or other portions of skin that are moist and frequently abraded. Hematogenous dissemination of these gram-positive organisms to the skin and soft tissue is uncommon except for *S. aureus* and some *Clostridium* species. A toxic shock–like syndrome has been described with blood stream infections caused by toxin-producing viridans streptococci, and diffuse erythroderma can be part of the early clinical presentation [170].

The foundation of the initial treatment of patients with neu-

Table 8. Skin and soft-tissue infections in the immune compromised host: treatment and management.

| Predisposing factor, pathogen | Type of therapy | Duration of therapy | Frequency or reason for surgery | Adjunct |
|-------------------------------|---|------------------------------------|---------------------------------|---|
| Neutropenia | | | | |
| Initial infection | | | | |
| Bacteria | | | | |
| Gram negative | Monotherapy or antibiotic combination | 7–14 days | Rare | G-CSF/GM-CSF; granulocyte therapy ^a |
| Gram positive | Pathogen specific | 7–10 days | Rare | No |
| Subsequent infection | | | | |
| Antibiotic-resistant bacteria | Pathogen specific | 7–14 days | Rare | G-CSF/GM-CSF; ^b granulocyte therapy ^a |
| Fungi | Amphotericin B, voriconazole, or caspofungin | Clinical and radiologic resolution | For localized infection | Catheter removal; G-CSF/GM-CSF; ^b granulocyte therapy ^a |
| Cellular immune deficiency | | | | |
| Bacteria | | | | |
| <i>Nocardia</i> species | Trimethoprim-sulfamethoxazole or sulfadiazine | 3–12 months | Rare | No |
| Atypical mycobacteria | Antibiotic combination (including a macrolide) | 3–6 weeks | Yes | No |
| Fungi | | | | |
| <i>Cryptococcus</i> species | Amphotericin B plus 5-fluorocytosine or fluconazole | 8–12 weeks | No | No |
| <i>Histoplasma</i> species | Amphotericin B or itraconazole | | | |
| Viruses | | | | |
| Varicella-zoster virus | Acyclovir famciclovir valacyclovir | 7–10 days | No | No |
| Herpes simplex virus | Acyclovir famciclovir valacyclovir | 7 days | No | No |
| Cytomegalovirus | Ganciclovir | 21 days | No | No |

NOTE. G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-monocyte colony-stimulating factor.

^a Use if gram-negative bacillary infection is unresponsive to appropriate antimicrobial therapy or if the patient has invasive fungal infection.

^b Progressive infection, pneumonia, and invasive fungal infection.

troponia is the administration of empirical, broad-spectrum antibiotics at the first clinical signs or symptoms of infection, including fever [159–161, 164, 165]. Antibiotic selection should follow the clinical care guidelines developed by the Infectious Diseases Society of America and the National Comprehensive Cancer Network [164, 165]. Excellent results have been reported for gram-negative infections using broad-spectrum monotherapy with carbapenems, cephalosporins that possess antipseudomonal activity, or piperacillin/tazobactam [164]. Antibiotic combinations using an aminoglycoside plus an antipseudomonal-penicillin or an extended-spectrum cephalosporin, or the combination of an extended-spectrum penicillin and ciprofloxacin, are also frequently recommended [164, 165].

Treatment of neutropenia-associated infections due to gram-positive organisms is now dictated by the increasing resistance of these pathogens, leading many clinicians to consider the empirical use of vancomycin as part of the initial antibiotic

regimen. This strategy, however, has no impact on the survival of adult patients with neutropenia-associated bloodstream infections due to gram-positive organisms [171], and because of the increasing prevalence of vancomycin-resistant organisms, current guidelines restrict the empirical use of this agent [164, 165]. Thus, if empirical vancomycin is administered, it should be discontinued if culture results remain negative after 72–96 h [164, 165]. Decisions regarding initial empirical antibiotic regimens and the subsequent antimicrobial adjustments, however, must consider adequate antimicrobial coverage against the more virulent gram-positive organisms (*S. aureus*, viridans streptococci, or antibiotic-resistant pathogens, such as MRSA, vancomycin-resistant enterococci, or penicillin-resistant *S. pneumoniae*.) [170, 172–175]. Linezolid or daptomycin may be acceptable alternatives to vancomycin. Linezolid is the drug of choice for infections caused by vancomycin-resistant enterococci, but potential hematologic toxicity and cost should limit

its use to individuals with pathogen-directed needs [176]. Although linezolid and daptomycin have US Food and Drug Administration approval for skin and soft-tissue infections, no prospective, randomized studies involving compromised patients have been performed.

Surgical intervention is rarely appropriate early during neutropenia-associated infection but may be necessary to drain a soft-tissue abscess after marrow recovery or for treatment of a progressive polymicrobial fasciitis. Most such infections do not require adjunct colony-stimulating factor therapy or granulocyte transfusions, but these therapies are often considered when infection progresses despite appropriate antimicrobial treatment [159–161, 176, 177].

Subsequent Infection in Neutropenic Patients

Subsequent infections are the major cause of infection-associated morbidity and mortality for patients with prolonged (duration, 7–10 days) and profound (<100 polymorphonuclear leukocytes/ μ L) neutropenia [159–161]. Of such patients, 25%–50% develop a second or subsequent episode of fever and/or infection [167]. Although the skin and soft tissues are less frequently infected (10%–15% of cases), they may represent an early site of infection dissemination. Among subsequent infections, 10%–15% are caused by antibiotic-resistant gram-negative bacilli, 30%–40% are caused by antibiotic-resistant gram-positive organisms (coagulase-negative staphylococci and vancomycin-resistant enterococci, most commonly), and >50% are caused by fungi [167]. Despite the incidence of subsequent infections caused by antibiotic-resistant gram-positive pathogens, the empirical administration of vancomycin is unjustified for patients with neutropenia and persistent fever (<96 h after initiation of empirical antibiotic therapy) who are clinically stable and have no identified site of infection [178]. Empirical antifungal therapy for patients with neutropenia and persistent fever remains a common clinical practice, as revealed by 2 clinical studies using amphotericin B that were conducted in the 1980s [179, 180]. Recently, 2 randomized, international, multicenter trials found that caspofungin [181] and voriconazole [182] were each suitable alternatives to amphotericin B in this patient population. Thus, profoundly neutropenic patients with persistent fever who are systemically ill despite empirical antibiotic therapy may benefit from empirical antifungal treatment (B-I).

Candida species. The frequency and occurrence of candidiasis has been well described [183, 184]. More than 80% of high-risk patients who develop neutropenia are colonized with *Candida* species, and superficial mucosal and cutaneous infections are common. These noninvasive infections can be effectively treated with improved skin care and a topical antifungal agent or with a short course systemic azole antibiotic (e.g., fluconazole). The incidence of invasive candidiasis before the

routine use of azole antifungal prophylaxis was reported to be as high as 12% for patients with profound and prolonged neutropenia or recipients of blood or bone marrow transplants [183]. *Candida albicans* (62% of candidiasis cases) and *Candida tropicalis* (21% of candidiasis cases) were most frequently isolated. Between 6% and 13% of patients with invasive candidiasis develop single or multiple nodular skin lesions [166, 183]. Such lesions are discrete, pink-to-red subcutaneous papules or nodules and are most commonly found on the trunk and extremities. The nodules are usually smaller (diameter, 0.5–0.8 cm) than ecthyma gangrenosum lesions, are initially nontender, and may evolve to develop central pallor; the nodules may become hemorrhagic in thrombocytopenic patients [160, 166]. Myositis can develop as a consequence of hematogenous infection and is most common with *C. tropicalis* infections [185, 186]. In these cases, pain is often the chief initial complaint. Muscle and soft-tissue abscess formation is uncommon, but when reported, it has usually followed bone marrow recovery.

Trichosporon beigelii. *T. beigelii* is an uncommon, but frequently fatal disseminated fungal infection that often involves the skin [187]. Dermatologic manifestations vary from multiple erythematous macules to maculopapular lesions, and analysis of tissue biopsy specimens reveals a mixture of true hyphae, pseudohyphae, budding yeast, and arthroconidia that can be easily mistaken for *Candida* species [166].

Aspergillus species. Infections due to *Aspergillus* species occur in 2%–10% of patients with profound and prolonged neutropenia, and they may be increasing in frequency [188, 189]. Mortality remains high for all of these infections [188, 190]. *Aspergillus fumigatus* is the most frequently isolated species (50% of cases), followed by *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus terreus* [188]. Isolation of *Aspergillus* species from blood cultures is infrequent, but dissemination to the brain, gastrointestinal tract, and other visceral organs is commonly revealed during autopsy [191]. Cutaneous infections are unusual, but they may occur secondary to hematogenous dissemination or locally at sites of intravenous catheter insertion or at nail bed and cuticle junctions on fingers and toes [192, 193]. Because *Aspergillus* organisms have a propensity for angioinvasion, they produce painful skin nodules that may rapidly become necrotic and resemble pyoderma gangrenosum lesions [166].

Rhizopus and Mucor species. Cutaneous infections due to organisms from the *Rhizopus* and *Mucor* genera are uncommon, but similar to infections due to *Aspergillus* species, epidermal and dermal necrosis may develop, because of the tendency of these organism to invade blood vessels. Skin lesions are usually erythematous, nodular, and tender. Local *Mucor* infections have occurred as a consequence of contaminated bandages or other skin trauma, but patients with pulmonary *Mucor* infection may also develop secondary cutaneous in-

involvement from presumed hematogenous dissemination [194, 195]. Disseminated infections are almost never associated with positive blood culture results, but even without a documented fungal bloodstream infection, the mortality rate for these infections remains very high [196].

Fusarium species. *Fusarium* species are now more frequently identified as the infecting pathogens in patients with prolonged and profound neutropenia [196–198]. Patients commonly have myalgias and persistent fever despite antimicrobial therapy. Skin lesions occur in 60%–80% of these infections and begin as multiple erythematous macules with central pallor that quickly evolve to papules and necrotic nodules. Lesions localize preferentially to the extremities but also occur on the face and trunk. Recovery of *Fusarium* species from blood cultures is common (40%–50% of cases) [191]. Mortality from this infection remains high among patients with persistent immunodeficiency, although the new azole antifungal agents appear to be promising [199].

The clinician must remember that yeast and fungal infections remain the primary cause of infection-associated death among patients with neutropenia or patients who undergo blood or bone marrow transplantation [200, 201]. Diagnosis of these infections remains difficult, and recovery of fungi from an aspiration or biopsy of skin or soft tissue almost always warrants aggressive therapy. Amphotericin B and lipid formulations of amphotericin B have been the gold standard of treatment, but newer antifungal agents, such as voriconazole and caspofungin, appear to be at least as effective against *Aspergillus* species, *Fusarium* species, and non-*albicans* species of *Candida* [164, 165, 184, 202–204]. All of the new antifungal agents have less serious acute toxicity and less nephrotoxicity but are also more expensive than conventional amphotericin B [203–208]. The importance of treatment with adjunct growth factor or granulocyte transfusion is unsubstantiated, but they are frequently considered for patients who remain profoundly neutropenic and unresponsive to antimicrobial therapy [177]. The routine use of azole prophylaxis in high-risk patients has dramatically decreased the incidence of invasive *C. albicans* infections but has increased the incidence of infections due to azole-resistant yeast, including *C. glabrata* or *C. krusei* [209].

Predisposition to Infections: Cellular Immune Deficiency

Patients with Hodgkin lymphoma or non-Hodgkin lymphoma; recipients of blood, marrow, or solid organ transplants; and patients being treated with corticosteroids and other immune suppressants are predisposed to infection because of abnormalities of their cellular (lymphocyte-mediated) immune function. These patients are at increased risk for infections, and the infections are caused by a select group of bacteria, fungi, viruses, protozoa, and helminthes, but only a few of these cause skin and soft-tissue infections (table 8). Some of these infections

arise from local skin inoculation, whereas others result from hematogenous dissemination.

Bacteria. Nontuberculous mycobacteria are ubiquitous, and most cutaneous mycobacteria infections occur after primary inoculation at sites of skin disruption or trauma, but hematogenous dissemination does occur [210–215]. Disseminated infection with *Mycobacterium avium* complex occurs preferentially among patients with HIV disease, whereas bloodstream infections with *Mycobacterium fortuitum*, *Mycobacterium chelonae*, *Mycobacterium abscessus*, *Mycobacterium ulcerans*, or *Mycobacterium mucogenicum* are more frequent among compromised hosts with indwelling vascular-access devices [216]. Sporadic cases in compromised hosts are also reported with *Mycobacterium kansasii*, *Mycobacterium haemophilum*, and *Mycobacterium marinum*. Dermatologic manifestations include a poorly resolving cellulitis, painless 1–2-cm nodules, necrotic ulcers, and subcutaneous abscesses.

Treatment of nontuberculous mycobacterial infections of the skin and soft tissues requires prolonged combination therapy (duration, 6–12 weeks) that should include a macrolide antibiotic (e.g., clarithromycin). Surgical debridement is appropriate and often necessary to remove devitalized tissue and to promote skin and soft-tissue healing [216].

Cutaneous *Nocardia* infections usually represent metastatic foci of infection from a primary pulmonary source. *Nocardia asteroides*, *Nocardia farcinica*, and *Nocardia brasiliensis* have been associated with cutaneous disease [217, 218]. The dermatologic manifestations are usually limited to subcutaneous nodules or abscess and panniculitis. Soft-tissue abscesses are frequently painless and are cold to the touch. The incidence of local and disseminated *Nocardia* infections has decreased with the routine use of trimethoprim-sulfamethoxazole prophylaxis for patients who experience prolonged periods of cellular immune deficiency.

Trimethoprim-sulfamethoxazole remains the treatment of choice [218], but other sulfa antibiotics (e.g., sulfadiazine and sulfasoxazole) or imipenem are effective. Prolonged therapy is important, and the duration of treatment (6–24 months) should take into account the presence of disseminated disease and the extent of the patient's underlying immune suppression. Surgical debridement is recommended for necrotic nodules or large subcutaneous abscesses.

Fungi. Cryptococcal infections originate in the lungs, often with early hematogenous dissemination to the meninges and skin or soft tissues [219], but primary cutaneous cryptococcus also occurs [220]. Single or multiple painless skin lesions involving the face and scalp develop in 5%–10% of clinically infected patients, and in some patients, these lesions may precede documented cryptococcal meningitis by several weeks. Cutaneous cryptococcal infections may appear as papules (often similar to molluscum contagiosum lesions), nodules, or pustules

or as chronic draining necrotic ulcers [220]. Cryptococcal cellulitis has occurred in recipients of blood, bone marrow, or solid organ transplants [221], although the incidence has dramatically decreased with the prophylactic use of the newer azole agents, particularly fluconazole. Fluconazole is often used as initial treatment, for patients with more mild infections, or to complete treatment after the patient has shown clinical and microbiologic improvement with amphotericin B and 5-flucytosine induction therapy [222, 223]. Surgical debridement and/or drainage are not helpful in the management of skin or soft-tissue cryptococcal infections [223].

Cutaneous manifestations of acute progressive disseminated histoplasmosis are rare [224] and usually occur in patients with severe cellular immune deficiency, where they appear as non-specific maculopapular eruptions that may become hemorrhagic. Oral ulcers sometimes present, particularly in the subacute, disseminated form of the disease. Histopathologic analysis of these skin lesions reveals necrosis surrounding the superficial dermal vessels, and with special stains, both intracellular and extracellular yeast may be seen. Prompt administration of amphotericin B therapy is the recommended treatment for patients with cellular immune deficiency and acute, life-threatening, progressive disseminated histoplasmosis [225]. Patients often show a rapid clinical improvement within 1–2 weeks, and itraconazole can then replace amphotericin B to complete at least 6–12 months of treatment. Patients with illnesses that result in profound and prolonged immune suppression should receive long-term suppressive therapy with itraconazole after the initial treatment course is complete.

Viruses. Varicella zoster virus (VZV) is one of the 2 most frequent herpesviruses to cause cutaneous infection in immunosuppressed patients [226–228]. Patients without a preceding history of varicella are at significant risk of developing the disease if exposed, but herpes zoster with or without dissemination is a more frequent clinical concern [227, 228]. Between 65% and 70% of adult patients are seropositive for VZV, and this identifies those patients at risk for future reactivation infection. Herpes zoster occurs most frequently during the first year after treatment, or after receipt of a blood, bone marrow, or a solid organ transplant [226, 229]. Depending on the intensity of treatment or type of transplantation, 25%–45% of such patients develop dermatomal zoster, with a 10%–20% risk of developing dissemination without prompt and effective antiviral therapy. A few patients present initially with disseminated cutaneous infection that mimics varicella. Herpes zoster (also known as “shingles”) causes a unilateral, vesicular eruption with dermatomal pain that often precedes the skin findings by 24–72 h (and sometimes longer). Early lesions are erythematous macules that rapidly evolve to papules and then to vesicles. The vesicles frequently coalesce, form bullae, and scab before healing. Lesions in otherwise healthy hosts continue to erupt

for at least 4–6 days, with the entire disease duration being <2 weeks. In immune suppressed hosts, lesions may continue to develop over a longer period (7–14 days) and generally heal more slowly unless effective antiviral therapy is administered [164, 165, 230, 231]. Without adequate treatment, some immune suppressed patients develop chronic ulcerations with persistent viral replication complicated by secondary bacterial and fungal superinfection. Disseminated VZV lesions characteristically begin on the face and trunk and then evolve peripherally. Cutaneous VZV, unlike smallpox, usually show lesions simultaneously in the varied stages of infection progression. Prevention of viral reactivation with oral acyclovir, famciclovir, or valacyclovir is an important component of the treatment of cutaneous VZV infection [164, 165]. Such therapy is usually administered to high-risk patients during the period of maximum immunosuppression. Recipients of an allogenic blood and bone marrow transplant routinely take acyclovir (800 mg twice per day) or valacyclovir (500 mg twice per day) during the first year after transplantation [165]. High-dose intravenous acyclovir remains the treatment of choice for VZV infections in compromised hosts [228] (B-III). Oral acyclovir, famciclovir, and valacyclovir are beneficial for VZV infections in otherwise healthy hosts, but oral therapy should probably be reserved for mild cases of VZV disease in patients with transient immune suppression or as treatment to complete therapy once the patient has shown a clinical response to intravenous acyclovir [165, 230, 231].

Herpes simplex virus (HSV) has a worldwide distribution, and >90% of adults have antibody to HSV-1 by the fifth decade of life [231, 232]. Antibodies against HSV-2 appear in puberty and correlate with sexual activity. The seroprevalence of HSV-2 antibody among patients in the United States is now 20%–25% [232, 233]. HSV infections in compromised hosts are almost exclusively due to viral reactivation [232]. Orofacial and genital sites are the most common cutaneous locations, but autoinoculation can occur in almost any area. Infections of the fingernail bed and cuticle (herpetic whitlow) occur because of inoculation of HSV at sites of epidermal surface breakdown. Cutaneous lesions are often preceded by localized pain or a tingling sensation. Early skin lesions are usually focal, erythematous, and maculopapular. These evolve to form thin-walled vesicles and then pustules before becoming small ulcers. Lesions frequently coalesce, and chronic, poorly healing ulcers are characteristic of HSV infections among immunocompromised hosts. These ulcerative lesions rarely include a vesicular component, thus making the clinical diagnosis of a chronic HSV infection more difficult. Bloodborne HSV dissemination, manifested by multiple vesicles over a widespread area of the trunk or extremities, is uncommon, but when seen among compromised hosts, it is usually secondary HSV-2 infection. Acyclovir is the treatment of choice for HSV infections, although fam-

ciclovir and valacyclovir are also highly effective [164, 165]. The development of acyclovir-resistant HSV isolates is well described and occurs more frequently among immune compromised patients [234]. Suppression of HSV reactivation or continued treatment until the ulcerated skin or mucosal lesions have totally healed may decrease the incidence of infections caused by acyclovir-resistant HSV strains. The treatment of acyclovir-resistant HSV isolates is a prolonged course of intravenous foscarnet [234]. Surgery should be avoided in patients with HSV infections, unless a documented bacterial or fungal abscess is identified.

Cutaneous cytomegalovirus infections have a highly variable appearance, including cutaneous nodules, ulcers, indurated plaques, maculopapular eruptions, and hemorrhagic vesicles. The true prevalence of these cutaneous infection is uncertain, because many have a bland appearance, biopsies are only rarely performed, and infection sites usually do not contain cells that demonstrate cytomegalovirus inclusions [235]. Prolonged ganciclovir therapy is the treatment of choice [165].

Parasites. Rarely, the skin and soft-tissue structures of immunosuppressed patients can also be affected by parasites, including but not limited to *Strongyloides stercoralis*, free-living amoeba (*Acanthamoeba* species and *Balamuthia* species), and *Sarcoptes scabiei*.

Infections Related to Iatrogenic Procedures

Many iatrogenic procedures disrupt the integumentary barrier and increase the risk of infection for immunocompromised patients. Vascular-access devices are the most common iatrogenic factor that predisposes patients to skin and soft-tissue infections, but many patients with intravenous catheters also have additional factors (e.g., neutropenia, cellular immunodeficiency, or humoral immunodeficiency) that increase their risk of infection. Intravenous vascular-access devices are almost universal for patients, such as blood, marrow, and solid organ transplant recipients, who are undergoing cancer therapy or in need of intensive care. These vascular devices allow administration of multiagent therapy, blood products, prolonged antimicrobial treatment, intravenous nutrition, and withdrawal of blood for monitoring and microbial evaluation. Many of these catheters remain in place for prolonged periods, and the risk of cutaneous infections varies with the device, the duration of catheter placement, and the severity of immune suppression. Cutaneous infections associated with catheter placement include the entry site infection (inflammation from the entry site to the first subcutaneous cuff), a tunnel infection (inflammation involving the skin and soft tissues that surround the catheter tunnel from the catheter cuff to the venous entrance), or vascular port-pocket infection. Tunnel and port-pocket infections are frequently accompanied by positive blood culture results (30%–40% of episodes), whereas blood culture results are rarely

positive when the catheter infection is limited to the entry site [164, 165, 236]. The skin manifestations of a tunnel infection include a painful cellulitis that may progress to necrosis or ulceration. Many early port-pocket infections are painless, hindering the clinician's ability to recognize the catheter as the site of infection. Gram-positive organisms cause two-thirds of the vascular device infections. Whereas coagulase-negative staphylococci are the most frequent pathogens, gram-negative bacilli, fungi, and atypical mycobacteria are other causes [165, 236]. The prevalence of infection due to gram-positive pathogens justifies recommending the use of empirical intravenous vancomycin for treatment of clinically serious catheter-associated infections [164, 165]. Most entry-site infections can be treated effectively with appropriate antimicrobial therapy without catheter removal [164, 165, 236]. Tunnel or port-pocket infections require catheter removal and culture, with modification of the empirical antimicrobial therapy on the basis of culture and susceptibility test results [165, 236]. Catheter-site infections caused by fungi or nontuberculosis mycobacteria routinely require catheter removal and debridement of devitalized soft tissues [211]. A recent report documented a 100% cure of tunnel infections caused by nontuberculous mycobacteria with combination antimicrobial therapy for 3–6 weeks plus catheter removal and debridement of the infected soft tissue [211].

Acknowledgments

Potential conflicts of interest. D.L.S. has received research funding from Wyeth, Lederle, Pfizer, Amgen, Roche, and Cubist and has served as a consultant for Schering Plough, Pfizer and Arpida. A.L.B. has served as a consultant for Merck, Cubist, Pharmacia, and Schering Plough. H.F.C. has received grant or research support from Ortho-McNeil and Cubist, has served as a consultant for or on the advisory board of Otho-McNeil and Osmotics, and has received honoraria from Basilea. P.D. has received grants for clinical research from, served on the advisory board of, and/or lectured for honoraria from GlaxoSmithKline, Bayer, Eli Lilly, Merck, Wyeth-Ayerst, Bristol-Myers Squibb, AstraZeneca, Pfizer, Aventis, Hoffman-La Roche, Arrow, Ortho-McNeil, Perke-Davis, Abbot, ICOS, Immunex, Chiron, Searle, Cubist, Virucon, InterMune, Peninsula, Johnson & Johnson, and BRAHMS. E.J.C.G. has served as a consultant for, on the speakers' bureau of, and/or has received research support from Merck, Aventis, Cubist, Bayer, Schering Plough, GlaxoSmithKline, Ortho-McNeil, and Vicuron and has served on the scientific advisory board of Merck, Bayer, and Schering Plough. J.G.M. has served on the speakers' bureau of Merck, Pfizer, Enzon, Aventis, and Schering Plough. All other authors: no conflicts.

References

1. Wong CH, Khin LW, Heng KS, Tan KC, Low CO. The LRINEC (Laboratory risk indicator for necrotizing fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. *Crit Care Med* 2004; 32:1535–41.
2. Thorell E, Jackson MA, Bratcher D, Swanson DS, Selvaragan R. Antimicrobial resistance of *Staphylococcus aureus* from Kansas City children: what is the appropriate current therapy for pediatric staphylococcal infections [abstract 252]? In: Proceedings and abstracts of the 42nd Annual Meeting of the Infectious Diseases Society of America

- (Boston). Alexandria, VA: Infectious Diseases Society of America, **2004**:81.
3. Ruhe JJ, Monson TP. Use of tetracyclines for infections caused by methicillin-resistant *Staphylococcus aureus* [abstract 516]. In: Proceedings and abstracts of the 42nd Annual Meeting of the Infectious Diseases Society of America (Boston). Alexandria, VA: Infectious Diseases Society of America, **2004**:139.
 4. Van Beneden CA, Facklam R, Lynfield R, Glennen A, Beall B, Whitney C. Erythromycin resistance among invasive group A streptococcal infections, United States, 1999–2001 [abstract 345]. In: Proceedings and abstracts of the 42nd Annual Meeting of the Infectious Diseases Society of America (Boston). Alexandria, VA: Infectious Diseases Society of America, **2004**:102.
 5. Yun HJ, Lee SW, Yoon GM, et al. Prevalence and mechanisms of low- and high-level mupirocin resistance in staphylococci isolated from a Korean hospital. *J Antimicrob Chemother* **2003**; *51*:619–23.
 6. Committee on Infectious Diseases, American Academy of Pediatrics. Antimicrobial agents and related therapy. In: Pickering LK, ed. Red book 2003 report of the Committee on Infectious Diseases. 26th ed. Elk Grove Village, IL: American Academy of Pediatrics, **2003**:693–4.
 7. Miller LG, Perdreaux-Remington F, Rieg G, et al. Necrotizing fasciitis caused by community-associated methicillin-resistant *Staphylococcus aureus* in Los Angeles. *N Engl J Med* **2005**; *352*:1445–53.
 8. Ferrieri P, Dajani AS, Wannamaker LW, Chapman SS. Natural history of impetigo. 1. Site sequence of acquisition and familial patterns of spread of cutaneous streptococci. *J Clin Invest* **1972**; *51*:2851–62.
 9. Adams BB. Dermatologic disorders of the athlete. *Sports Med* **2002**; *32*:309–21.
 10. Fehrs LJ, Flanagan K, Kline S, Facklam RR, Quackenbush K, Foster LR. Group A beta-hemolytic streptococcal skin infections in a US meat-packing plant. *JAMA* **1987**; *258*:3131–4.
 11. Hirschmann JV. Impetigo: etiology and therapy. *Curr Clin Top Infect Dis* **2002**; *22*:42–51.
 12. Darmstadt GL, Lane AT. Impetigo: an overview. *Pediatr Dermatol* **1994**; *11*:293–303.
 13. Demidovich CW, Wittler RR, Ruff ME, Bass JW, Browning WC. Impetigo: current etiology and comparison of penicillin, erythromycin, and cephalixin therapies. *Am J Dis Child* **1990**; *144*:1313–5.
 14. Kaplan EL, Anthony BF, Chapman SS, Ayoub EM, Wannamaker LW. The influence of the site of infection on the immune response to group A streptococci. *J Clin Invest* **1970**; *49*:1405–14.
 15. Bisno AL, Nelson KE, Waytz P, Brunt J. Factors influencing serum antibody response in streptococcal pyoderma. *J Lab Clin Med* **1973**; *81*:410–20.
 16. Kaplan EL, Wannamaker LW. Suppression of the anti-streptolysin O response by cholesterol and by lipid extracts of rabbit skin. *J Exp Med* **1976**; *144*:754–67.
 17. Derrick CW Jr, Dillon HC Jr. Impetigo contagiosa. *Am Fam Physician* **1971**; *4*:75–81.
 18. Ferrieri P, Dajani AS, Wannamaker LW. A controlled study of penicillin prophylaxis against streptococcal impetigo. *J Infect Dis* **1974**; *129*:429–38.
 19. Dagan R, Bar-David Y. Comparison of amoxicillin and clavulanic acid (augmentin) for the treatment of nonbullous impetigo. *Am J Dis Child* **1989**; *143*:916–8.
 20. Barton LL, Friedman AD. Impetigo: a reassessment of etiology and therapy. *Pediatr Dermatol* **1987**; *4*:185–8.
 21. Barton LL, Friedman AD, Sharkey AM, Schneller DJ, Swierkosz EM. Impetigo contagiosa III: comparative efficacy of oral erythromycin and topical mupirocin. *Pediatr Dermatol* **1989**; *6*:134–8.
 22. Britton JW, Fajardo JE, Krafte-Jacobs B. Comparison of mupirocin and erythromycin in the treatment of impetigo. *J Pediatr* **1990**; *117*:827–9.
 23. Weinstein L, Le Frock J. Does antimicrobial therapy of streptococcal pharyngitis or pyoderma alter the risk of glomerulonephritis? *J Infect Dis* **1971**; *124*:229–31.
 24. Meislin HW, Lerner SA, Graves MH, et al. Cutaneous abscesses: aerobic and aerobic bacteriology and outpatient management. *Ann Intern Med* **1977**; *87*:145–9.
 25. Ghoneim AT, McGoldrick J, Blick PW, Flowers MW, Marsden AK, Wilson DH. Aerobic and anaerobic bacteriology of subcutaneous abscesses. *Br J Surg* **1981**; *68*:498–500.
 26. Brook I, Frazier EH. Aerobic and anaerobic bacteriology of wounds and cutaneous abscesses. *Arch Surg* **1990**; *125*:1445–51.
 27. Leach RD, Eykyn SJ, Phillips I, Corrin B, Taylor EA. Anaerobic axillary abscess. *Br Med J* **1979**; *2*:5–7.
 28. Whitehead SM, Leach RD, Eykyn SJ, Phillips I. The aetiology of scrotal sepsis. *Br J Surg* **1982**; *69*:729–30.
 29. Edmiston CE Jr, Walker AP, Krepel CJ, Gohr C. The nonpuerperal breast infection: aerobic and anaerobic microbial recovery from acute and chronic disease. *J Infect Dis* **1990**; *162*:695–9.
 30. Whitehead SM, Leach RD, Eykyn SJ, Phillips I. The aetiology of perirectal sepsis. *Br J Surg* **1982**; *69*:166–8.
 31. Diven DG, Dozier SE, Meyer DJ, Smith EB. Bacteriology of inflamed and uninfamed epidermal inclusion cysts. *Arch Dermatol* **1998**; *134*:49–51.
 32. Llera JL, Levy RC. Treatment of cutaneous abscess: a double-blind clinical study. *Ann Emerg Med* **1985**; *14*:15–9.
 33. Macfie J, Harvey J. The treatment of acute superficial abscesses: a prospective clinical trial. *Br J Surg* **1977**; *64*:264–6.
 34. Decker MD, Lybarger JA, Vaughn WK, Hutcheson RH Jr, Schaffner W. An outbreak of staphylococcal skin infections among river rafting guides. *Am J Epidemiol* **1986**; *124*:969–76.
 35. Sosin DM, Gunn RA, Ford WL, Skaggs JW. An outbreak of furunculosis among high school athletes. *Am J Sports Med* **1989**; *17*:828–32.
 36. Zimakoff J, Rosdahl VT, Petersen W, Scheibel J. Recurrent staphylococcal furunculosis in families. *Scand J Infect Dis* **1988**; *20*:403–5.
 37. Hedstrom SA. Recurrent staphylococcal furunculosis: bacteriological findings and epidemiology in 100 cases. *Scand J Infect Dis* **1981**; *13*:115–9.
 38. Raz R, Miron D, Colodner R, Staler Z, Samara Z, Keness Y. A 1-year trial of nasal mupirocin in the prevention of recurrent staphylococcal nasal colonization and skin infection. *Arch Intern Med* **1996**; *156*:1109–12.
 39. Lipsky BA, Pecoraro RE, Ahroni JH, Peugeot RL. Immediate and long-term efficacy of systemic antibiotics for eradicating nasal colonization with *Staphylococcus aureus*. *Eur J Clin Microbiol Infect Dis* **1992**; *11*:43–7.
 40. Klemmner MS, Styrt B. Prevention of recurrent staphylococcal skin infections with low-dose oral clindamycin therapy. *JAMA* **1988**; *260*:2682–5.
 41. Bisno AL, Stevens DL. Streptococcal infections in skin and soft tissues. *N Engl J Med* **1996**; *334*:240–5.
 42. Chartier C, Grosshans E. Erysipelas. *Int J Dermatol* **1990**; *29*:459–67.
 43. Chartier C, Grosshans E. Erysipelas: an update. *Int J Dermatol* **1996**; *35*:779–81.
 44. Swartz MN. Clinical practice: cellulitis. *N Engl J Med* **2004**; *350*:904–12.
 45. Bernard P, Plantin P, Roger H, et al. Roxithromycin versus penicillin in the treatment of erysipelas in adults: a comparative study. *Br J Dermatol* **1992**; *127*:155–9.
 46. Martin JM, Green M, Barbadora KA, Wald ER. Erythromycin-resistant group A streptococci in schoolchildren in Pittsburgh. *N Engl J Med* **2002**; *346*:1200–6.
 47. York MK, Gibbs L, Perdreaux-Remington F, Brooks GF. Characterization of antimicrobial resistance in *Streptococcus pyogenes* isolates from the San Francisco Bay area of northern California. *J Clin Microbiol* **1999**; *37*:1727–31.
 48. Dupuy A, Benchikhi H, Roujeau JC, et al. Risk factors for erysipelas of the leg (cellulitis): case-control study. *BMJ* **1999**; *318*:1591–4.
 49. Dan M, Heller K, Shapira I, Vidne B, Shibolet S. Incidence of erysipelas following venectomy for coronary artery bypass surgery. *Infection* **1987**; *15*:107–8.

50. Baddour LM, Bisno AL. Recurrent cellulitis after saphenous venectomy for coronary bypass surgery. *Ann Intern Med* **1982**;97:493–6.
51. Simon MS, Cody RL. Cellulitis after axillary lymph node dissection for carcinoma of the breast. *Am J Med* **1992**;93:543–8.
52. Baddour LM. Breast cellulitis complicating breast conservation therapy. *J Intern Med* **1999**;245:5–9.
53. Bouma J, Dankert J. Recurrent acute leg cellulitis in patients after radical vulvectomy. *Gynecol Oncol* **1988**;29:50–7.
54. Dankert J, Bouma J. Recurrent acute leg cellulitis after hysterectomy with pelvic lymphadenectomy. *Br J Obstet Gynaecol* **1987**;94:788–90.
55. Perl B, Gottehrer NP, Raveh D, Schlesinger Y, Rudensky B, Yinnon AM. Cost-effectiveness of blood cultures for adult patients with cellulitis. *Clin Infect Dis* **1999**;29:1483–8.
56. Kielhofner MA, Brown B, Dall L. Influence of underlying disease process on the utility of cellulitis needle aspirates. *Arch Intern Med* **1988**;148:2451–2.
57. Hook EW III, Hooton TM, Horton CA, Coyle MB, Ramsey PG, Turck M. Microbiologic evaluation of cutaneous cellulitis in adults. *Arch Intern Med* **1986**;146:295–7.
58. Sachs MK. The optimum use of needle aspiration in the bacteriologic diagnosis of cellulitis in adults. *Arch Intern Med* **1990**;150:1907–12.
59. Leppard BJ, Seal DV, Colman G, Hallas G. The value of bacteriology and serology in the diagnosis of cellulitis and erysipelas. *Br J Dermatol* **1985**;112:559–67.
60. Sigurdsson AF, Gudmundsson S. The etiology of bacterial cellulitis as determined by fine-needle aspiration. *Scand J Infect Dis* **1989**;21:537–42.
61. Newell PM, Norden CW. Value of needle aspiration in bacteriologic diagnosis of cellulitis in adults. *J Clin Microbiol* **1988**;26:401–4.
62. Lebre C, Girard-Pipau F, Roujeau JC, Revuz J, Saiag P, Chosidow O. Value of fine-needle aspiration in infectious cellulitis. *Arch Dermatol* **1996**;132:842–3.
63. Lutomski DM, Trott AT, Runyon JM, Miyagawa CI, Staneck JL, Rivera JO. Microbiology of adult cellulitis. *J Fam Pract* **1988**;26:45–8.
64. Duvanel T, Auckenthaler R, Rohner P, Harms M, Saurat JH. Quantitative cultures of biopsy specimens from cutaneous cellulitis. *Arch Intern Med* **1989**;149:293–6.
65. Eriksson B, Jorup-Ronstrom C, Karkkonen K, Sjoblom AC, Holm SE. Erysipelas: clinical and bacteriologic spectrum and serological aspects. *Clin Infect Dis* **1996**;23:1091–8.
66. Bernard P, Toty L, Mounier M, Denis F, Bonnetblanc JM. Early detection of streptococcal group antigens in skin samples by latex particle agglutination. *Arch Dermatol* **1987**;123:468–70.
67. Bernard P, Bedane C, Mounier M, Denis F, Catanzano G, Bonnetblanc JM. Streptococcal cause of erysipelas and cellulitis in adults: a microbiologic study using a direct immunofluorescence technique. *Arch Dermatol* **1989**;125:779–82.
68. Baddour LM, Bisno AL. Recurrent cellulitis after coronary bypass surgery. Association with superficial fungal infection in saphenous venectomy limbs. *JAMA* **1984**;251:1049–52.
69. Semel JD, Goldin H. Association of athlete's foot with cellulitis of the lower extremities: diagnostic value of bacterial cultures of ipsilateral interdigital space samples. *Clin Infect Dis* **1996**;23:1162–4.
70. Eriksson BK. Anal colonization of group G β -hemolytic streptococci in relapsing erysipelas of the lower extremity. *Clin Infect Dis* **1999**;29:1319–20.
71. Burman WJ, Cohn DL, Reves RR, Wilson ML. Multifocal cellulitis and monoarticular arthritis as manifestations of *Helicobacter cinaedi* bacteremia. *Clin Infect Dis* **1995**;20:564–70.
72. Kirsner RS, Pardes JB, Eaglstein WH, Falanga V. The clinical spectrum of lipodermatosclerosis. *J Am Acad Dermatol* **1993**;28:623–7.
73. Jorup-Ronstrom C, Britton S, Gavlevik A, Gunnarsson K, Redman AC. The course, costs, and complications of oral versus intravenous penicillin therapy of erysipelas. *Infection* **1984**;12:390–4.
74. Hepburn MJ, Dooley DP, Skidmore PJ, Ellis MW, Starnes WF, Hasewinkle WC. Comparison of short-course (5 days) and standard (10 days) treatment for uncomplicated cellulitis. *Arch Intern Med* **2004**;164:1669–74.
75. Bergkvist PI, Sjobeck K. Antibiotic and prednisolone therapy of erysipelas: a randomized, double blind, placebo-controlled study. *Scand J Infect Dis* **1997**;29:377–82.
76. Bergkvist PI, Sjobeck K. Relapse of erysipelas following treatment with prednisolone or placebo in addition to antibiotics: a 1-year follow-up. *Scand J Infect Dis* **1998**;30:206–7.
77. Babb RR, Spittell JA Jr, Martin WJ, Schirger A. Prophylaxis of recurrent lymphangitis complicating lymphedema. *JAMA* **1966**;195:871–3.
78. Kremer M, Zuckerman R, Avraham Z, Raz R. Long-term antimicrobial therapy in the prevention of recurrent soft-tissue infections. *J Infect* **1991**;22:37–40.
79. Sjoblom AC, Eriksson B, Jorup-Ronstrom C, Karkkonen K, Lindqvist M. Antibiotic prophylaxis in recurrent erysipelas. *Infection* **1993**;21:390–3.
80. Wang JH, Liu YC, Cheng DL, et al. Role of benzathine penicillin G in prophylaxis for recurrent streptococcal cellulitis of the lower legs. *Clin Infect Dis* **1997**;25:685–9.
81. Kasseroller R. Sodium selenite as prophylaxis against erysipelas in secondary lymphedema. *Anticancer Res* **1998**;18:2227–30.
82. Groom AV, Wolsey DH, Naimi TS, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* in a rural American Indian community. *JAMA* **2001**;286:1201–5.
83. Herold BC, Immergluck LC, Maranan MC, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* in children with no identified predisposing risk. *JAMA* **1998**;279:593–8.
84. Centers for Disease Control and Prevention. Outbreaks of community-associated methicillin-resistant *Staphylococcus aureus* skin infections—Los Angeles County, California, 2002–2003. *MMWR Morb Mortal Wkly Rep* **2003**;52:88.
85. Ma XX, Ito T, Tiensasitorn C, et al. Novel type of staphylococcal cassette chromosome mec identified in community-acquired methicillin-resistant *Staphylococcus aureus* strains. *Antimicrob Agents Chemother* **2002**;46:1147–52.
86. Okuma K, Iwakawa K, Turnidge JD, et al. Dissemination of new methicillin-resistant *Staphylococcus aureus* clones in the community. *J Clin Microbiol* **2002**;40:4289–94.
87. Dufour P, Gillet Y, Bes M, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* infections in France: emergence of a single clone that produces Panton-Valentine leukocidin. *Clin Infect Dis* **2002**;35:819–24.
88. Methicillin-resistant *Staphylococcus aureus* infections in correctional facilities—Georgia, California, and Texas, 2001–2003. *MMWR Morb Mortal Wkly Rep* **2003**;52:992–6.
89. Methicillin-resistant *Staphylococcus aureus* infections among competitive sports participants—Colorado, Indiana, Pennsylvania, and Los Angeles County, 2000–2003. *MMWR Morb Mortal Wkly Rep* **2003**;52:793–5.
90. Stevens DL, Smith LG, Bruss JB, et al. Randomized comparison of linezolid (PNU-100766) versus oxacillin-dicloxacillin for treatment of complicated skin and soft tissue infections. *Antimicrob Agents Chemother* **2000**;44:3408–13.
91. Stevens DL, Herr D, Lampiris H, Hunt JL, Batts DH, Hafkin B. Linezolid versus vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* infections. Linezolid MRSA Study Group. *Clin Infect Dis* **2002**;34:1481–90.
92. Markowitz N, Quinn EL, Saravolatz LD. Trimethoprim-sulfamethoxazole compared with vancomycin for the treatment of *Staphylococcus aureus* infection. *Ann Intern Med* **1992**;117:390–8.
93. Ahrenholz DH. Necrotizing soft-tissue infections. *Surg Clin North Am* **1988**;68:199–214.
94. Lewis RT. Necrotizing soft-tissue infections. *Infect Dis Clin North Am* **1992**;6:693–703.
95. Rea WJ, Wyrick WJ Jr. Necrotizing fasciitis. *Ann Surg* **1970**;172:957–64.

96. Giuliano A, Lewis F Jr, Hadley K, Blaisdell FW. Bacteriology of necrotizing fasciitis. *Am J Surg* **1977**; 134:52–7.
97. Stevens DL, Tanner MH, Winship J, et al. Reappearance of scarlet fever toxin A among streptococci in the Rocky Mountain West: severe group A streptococcal infections associated with a toxic shock-like syndrome. *N Engl J Med* **1989**; 321:1–7.
98. Chelsom J, Halstensen A, Haga T, Hoiby EA. Necrotising fasciitis due to group A streptococci in western Norway: incidence and clinical features. *Lancet* **1994**; 344:1111–5.
99. Zimbelman J, Palmer A, Todd J. Improved outcome of clindamycin compared with beta-lactam antibiotic treatment for invasive *Streptococcus pyogenes* infection. *Pediatr Infect Dis J* **1999**; 18:1096–100.
100. Mulla ZD, Leaverton PE, Wiersma ST. Invasive group A streptococcal infections in Florida. *South Med J* **2003**; 96:968–73.
101. Stevens DL. Dilemmas in the treatment of invasive *Streptococcus pyogenes* infections. *Clin Infect Dis* **2003**; 37:341–3.
102. Kaul R, McGeer A, Norrby-Teglund A, et al. Intravenous immunoglobulin therapy for streptococcal toxic shock syndrome: a comparative observational study. *Clin Infect Dis* **1999**; 28:800–7.
103. Darenberg J, Ihendyane N, Sjolín J, et al. Intravenous immunoglobulin G therapy in streptococcal toxic shock syndrome: a European randomized, double-blind, placebo-controlled trial. *Clin Infect Dis* **2003**; 37:333–40.
104. Sissolak D, Weir WR. Tropical pyomyositis. *J Infect* **1994**; 29:121–7.
105. Laucks SS. Fournier's gangrene. *Surg Clin North Am* **1994**; 74:1339–52.
106. Eke N. Fournier's gangrene: a review of 1726 cases. *Br J Surg* **2000**; 87:718–28.
107. Altemeier WA, Fullen WD. Prevention and treatment of gas gangrene. *JAMA* **1971**; 217:806–13.
108. Stevens DL, Laine BM, Mitten JE. Comparison of single and combination antimicrobial agents for prevention of experimental gas gangrene caused by *Clostridium perfringens*. *Antimicrob Agents Chemother* **1987**; 31:312–6.
109. Stevens DL, Maier KA, Laine BM, Mitten JE. Comparison of clindamycin, rifampin, tetracycline, metronidazole, and penicillin for efficacy in prevention of experimental gas gangrene due to *Clostridium perfringens*. *J Infect Dis* **1987**; 155:220–8.
110. Stevens DL, Bryant AE, Adams K, Mader JT. Evaluation of hyperbaric oxygen therapy for treatment of experimental *Clostridium perfringens* infection. *Clin Infect Dis* **1993**; 17:231–7.
111. Talan DA, Citron DM, Abrahamian FM, Moran GJ, Goldstein EJ. Bacteriologic analysis of infected dog and cat bites. Emergency Medicine Animal Bite Infection Study Group. *N Engl J Med* **1999**; 340:85–92.
112. Goldstein EJ, Citron DM, Wield B, et al. Bacteriology of human and animal bite wounds. *J Clin Microbiol* **1978**; 8:667–72.
113. Goldstein EJ. New horizons in the bacteriology, antimicrobial susceptibility and therapy of animal bite wounds. *J Med Microbiol* **1998**; 47:95–7.
114. Goldstein EJ, Reinhardt JF, Murray PM, Finegold SM. Outpatient therapy of bite wounds: demographic data, bacteriology, and a prospective, randomized trial of amoxicillin/clavulanic acid versus penicillin +/- dicloxacillin. *Int J Dermatol* **1987**; 26:123–7.
115. Talan DA, Abrahamian FM, Moran GJ, Citron DM, Tan JO, Goldstein EJ. Clinical presentation and bacteriologic analysis of infected human bites in patients presenting to emergency departments. *Clin Infect Dis* **2003**; 37:1481–9.
116. Transmission of HIV by human bite. *Lancet* **1987**; 2:522.
117. Vidmar L, Poljak M, Tomazic J, Seme K, Klavs I. Transmission of HIV-1 by human bite. *Lancet* **1996**; 347:1762.
118. Dusheiko GM, Smith M, Scheuer PJ. Hepatitis C virus transmitted by human bite. *Lancet* **1990**; 336:503–4.
119. Davis LG, Weber DJ, Lemon SM. Horizontal transmission of hepatitis B virus. *Lancet* **1989**; 1:889–93.
120. Fiumara NJ, Exner JH. Primary syphilis following a human bite. *Sex Transm Dis* **1981**; 8:21–2.
121. Inglesby TV, Henderson DA, Bartlett JG, et al. Anthrax as a biological weapon: medical and public health management. Working Group on Civilian Biodefense. *JAMA* **1999**; 281:1735–45.
122. Dixon TC, Meselson M, Guillemin J, Hanna PC. Anthrax. *N Engl J Med* **1999**; 341:815–26.
123. Update: investigation of bioterrorism-related anthrax and interim guidelines for exposure management and antimicrobial therapy, October 2001. *MMWR Morb Mortal Wkly Rep* **2001**; 50:909–19.
124. Bass JW, Freitas BC, Freitas AD, et al. Prospective randomized double blind placebo-controlled evaluation of azithromycin for treatment of cat-scratch disease. *Pediatr Infect Dis J* **1998**; 17:447–52.
125. Reboli AC, Farrar WE. *Erysipelothrix rhusiopathiae*: an occupational pathogen. *Clin Microbiol Rev* **1989**; 2:354–9.
126. Venditti M, Gelfusa V, Tarasi A, Brandimarte C, Serra P. Antimicrobial susceptibilities of *Erysipelothrix rhusiopathiae*. *Antimicrob Agents Chemother* **1990**; 34:2038–40.
127. Srinivasan A, Kraus CN, DeShazer D, et al. Glanders in a military research microbiologist. *N Engl J Med* **2001**; 345:256–8.
128. Perry RD, Fetherston JD. *Yersinia pestis*—etiologic agent of plague. *Clin Microbiol Rev* **1997**; 10:35–66.
129. Inglesby TV, Dennis DT, Henderson DA, et al. Plague as a biological weapon: medical and public health management. Working Group on Civilian Biodefense. *JAMA* **2000**; 283:2281–90.
130. Enderlin G, Morales L, Jacobs RF, Cross JT. Streptomycin and alternative agents for the treatment of tularemia: review of the literature. *Clin Infect Dis* **1994**; 19:42–7.
131. Johansson A, Berglund L, Gothefors L, Sjostedt A, Tarnvik A. Ciprofloxacin for treatment of tularemia in children. *Pediatr Infect Dis J* **2000**; 19:449–53.
132. Chocarro A, Gonzalez A, Garcia I. Treatment of tularemia with ciprofloxacin. *Clin Infect Dis* **2000**; 31:623.
133. Perez-Castrillon JL, Bachiller-Luque P, Martin-Luquero M, Mena-Martin FJ, Herreros V. Tularemia epidemic in northwestern Spain: clinical description and therapeutic response. *Clin Infect Dis* **2001**; 33:573–6.
134. Brennan TA, Leape LL, Laird NM, et al. Incidence of adverse events and negligence in hospitalized patients: results of the Harvard Medical Practice Study I. *N Engl J Med* **1991**; 324:370–6.
135. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999: Hospital Infection Control Practices Advisory Committee. *Infect Control Hosp Epidemiol* **1999**; 20:250–78.
136. Gaynes RP, Culver DH, Horan TC, Edwards JR, Richards C, Tolson JS. Surgical site infection (SSI) rates in the United States, 1992–1998: the National Nosocomial Infections Surveillance System basic SSI risk index. *Clin Infect Dis* **2001**; 33(Suppl 2):S69–S77.
137. Dellinger EP. Approach to the patient with postoperative fever. In: Gorbach SL, Bartlett JG, Blacklow NR, eds. *Infectious diseases in medicine and surgery*. Philadelphia: W. B. Saunders, **1998**:903–9.
138. Burke JF. The effective period of preventive antibiotic action in experimental incisions and dermal lesions. *Surgery* **1961**; 50:161–8.
139. Classen DC, Evans RS, Pestotnik SL, Horn SD, Menlove RL, Burke JP. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. *N Engl J Med* **1992**; 326:281–6.
140. Stone HH, Haney BB, Kolb LD, Geheber CE, Hooper CA. Prophylactic and preventive antibiotic therapy: timing, duration and economics. *Ann Surg* **1979**; 189:691–9.
141. Dellinger EP, Gross PA, Barrett TL, et al. Quality standard for antimicrobial prophylaxis in surgical procedures. Infectious Diseases Society of America. *Clin Infect Dis* **1994**; 18:422–7.
142. Bratzler DW, Houck PM. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. *Clin Infect Dis* **2004**; 38:1706–15.
143. McDonald M, Grabsch E, Marshall C, Forbes A. Single- versus multiple-dose antimicrobial prophylaxis for major surgery: a systematic review. *Aust N Z J Surg* **1998**; 68:388–96.

144. Bartlett P, Reingold AL, Graham DR, et al. Toxic shock syndrome associated with surgical wound infections. *JAMA* **1982**;247:1448–50.
145. Raab MG, O'Brien M, Hayes JM, Graham DR. Postoperative toxic shock syndrome. *Am J Orthop* **1995**;24:130–6.
146. Huizinga WK, Kritzing NA, Bhamjee A. The value of adjuvant systemic antibiotic therapy in localised wound infections among hospital patients: a comparative study. *J Infect* **1986**;13:11–6.
147. Mandell GL, Bennett JE, Dolin R. Mandell, Douglas and Bennett's principles and practice of infectious diseases. New York: Churchill Livingstone, **1995**.
148. Howard RJ. Surgical infectious diseases. Norwalk: Appleton & Lange, **1988**.
149. Fry DE. Surgical infections. Boston: Little, Brown and Company, **1995**.
150. Greenfield LJ, Mulholland MW, Oldham KT, Zelenock GB. Surgery: scientific principles and practice. Philadelphia: J. B. Lippincott Company, **1993**.
151. Townsend CM Jr, Beauchamp RD, Evers BM, Mattox KL, Sabiston S. Textbook of surgery: the biologic basis of modern surgical practice. Philadelphia: W. B. Saunders and Company, **2001**.
152. Wilmore DW, Cheung LY, Harken AH, Holcroft JW, Meakins JL, Soper NJ. ACS surgery: principles and practice. New York: WebMD, **2002**.
153. Gorbach SL, Bartlett JG, Blacklow NR. Infectious diseases. Philadelphia: W. B. Saunders and Company, **1998**.
154. Dellinger EP. Nosocomial infection. In: Wilmore DW, Cheung LY, Harken AH, Holcroft JW, Meakins JL, Soper NJ, eds. ACS surgery: principles and practice. New York: WebMD, **2002**:1221–38.
155. Cruse PJE. Wound infections: epidemiology and clinical characteristics. In: Howard RJ, Simmons RL, eds. Surgical infectious diseases. Norwalk: Appleton & Lange, **1988**:319–29.
156. Bobrow BJ, Pollack CV Jr, Gamble S, Seligson RA. Incision and drainage of cutaneous abscesses is not associated with bacteremia in afebrile adults. *Ann Emerg Med* **1997**;29:404–8.
157. Meislin HW. Pathogen identification of abscesses and cellulitis. *Ann Emerg Med* **1986**;15:329–32.
158. Dellinger EP. Postoperative wound infection. In: Schlossberg D, ed. Current therapy of infectious disease. St. Louis: Mosby, **1996**:337–9.
159. Wade JC. Management of infection in patients with acute leukemia. *Hematol Oncol Clin North Am* **1993**;7:293–315.
160. Pizzo PA. Management of fever in patients with cancer and treatment-induced neutropenia. *N Engl J Med* **1993**;328:1323–32.
161. Donowitz GR. Fever in the compromised host. *Infect Dis Clin North Am* **1996**;10:129–48.
162. Wolfson JS, Sober AJ, Rubin RH. Dermatologic manifestations of infections in immunocompromised patients. *Medicine (Baltimore)* **1985**;64:115–33.
163. Wolfson JS, Sober AJ, Rubin RH. Dermatologic manifestations of infection in the compromised host. *Annu Rev Med* **1983**;34:205–17.
164. Hughes WT, Armstrong D, Bodey GP, et al. 2002 Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* **2002**;34:730–51.
165. NCCN practice guidelines for fever and neutropenia. National Comprehensive Cancer Network. Oncology (Williston Park) **1999**;13:197–257.
166. Lopez FA, Sanders CV. Dermatologic infections in the immunocompromised (non-HIV) host. *Infect Dis Clin North Am* **2001**;15:671–702, xi.
167. Wingard JR, Santos GW, Saral R. Differences between first and subsequent fevers during prolonged neutropenia. *Cancer* **1987**;59:844–9.
168. Chatzinikolaou I, Abi-Said D, Bodey GP, Rolston KV, Tarrand JJ, Samonis G. Recent experience with *Pseudomonas aeruginosa* bacteremia in patients with cancer: retrospective analysis of 245 episodes. *Arch Intern Med* **2000**;160:501–9.
169. Glauser M. Empiric therapy of bacterial infections in patients with severe neutropenia. *Diagn Microbiol Infect Dis* **1998**;31:467–72.
170. Elting LS, Bodey GP, Keefe BH. Septicemia and shock syndrome due to viridans streptococci: a case-control study of predisposing factors. *Clin Infect Dis* **1992**;14:1201–7.
171. European Organization for Research and Treatment of Cancer (EORTC) International Antimicrobial Therapy Cooperative Group and the National Cancer Institute of Canada-Clinical Trials Group. Vancomycin added to empirical combination antibiotic therapy for fever in granulocytopenic cancer patients. *J Infect Dis* **1991**;163:951–8.
172. Edmond MB, Ober JF, Dawson JD, Weinbaum DL, Wenzel RP. Vancomycin-resistant enterococcal bacteremia: natural history and attributable mortality. *Clin Infect Dis* **1996**;23:1234–9.
173. Martin MA, Pfaller MA, Wenzel RP. Coagulase-negative staphylococcal bacteremia: mortality and hospital stay. *Ann Intern Med* **1989**;110:9–16.
174. Wenzel RP. Perspective: attributable mortality—the promise of better antimicrobial therapy. *J Infect Dis* **1998**;178:917–9.
175. Brown AE, Kiehn TE, Armstrong D. Bacterial resistance in the patient with neoplastic disease. *Infect Dis Clin Pract* **1995**;4(Suppl 3):S136–44.
176. Rubinstein E, Cammarata S, Oliphant T, Wunderink R. Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. *Clin Infect Dis* **2001**;32:402–12.
177. Ozer H, Armitage JO, Bennett CL, et al. 2000 Update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. American Society of Clinical Oncology Growth Factors Expert Panel. *J Clin Oncol* **2000**;18:3558–85.
178. Cometta A, Kern WV, De Bock R, et al. Vancomycin versus placebo for treating persistent fever in patients with neutropenic cancer receiving piperacillin-tazobactam monotherapy. *Clin Infect Dis* **2003**;37:382–9.
179. Pizzo PA, Robichaud KJ, Gill FA, Witebsky FG. Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. *Am J Med* **1982**;72:101–11.
180. EORTC International Antimicrobial Therapy Cooperative Group. Empiric antifungal therapy in febrile granulocytopenic patients. *Am J Med* **1989**;86:668–72.
181. Walsh TJ, Tepler H, Donowitz GR, et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. *N Engl J Med* **2004**;351:1391–402.
182. Walsh TJ, Pappas P, Winston DJ, et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med* **2002**;346:225–34.
183. Goodrich JM, Reed EC, Mori M, et al. Clinical features and analysis of risk factors for invasive candidal infection after marrow transplantation. *J Infect Dis* **1991**;164:731–40.
184. Rex JH, Walsh TJ, Sobel JD, et al. Practice guidelines for the treatment of candidiasis. Infectious Diseases Society of America. *Clin Infect Dis* **2000**;30:662–78.
185. Wingard JR, Merz WG, Saral R. *Candida tropicalis*: a major pathogen in immunocompromised patients. *Ann Intern Med* **1979**;91:539–43.
186. Jarowski CI, Fialk MA, Murray HW, et al. Fever, rash, and muscle tenderness: a distinctive clinical presentation of disseminated candidiasis. *Arch Intern Med* **1978**;138:544–6.
187. Walsh TJ, Newman KR, Moody M, Wharton RC, Wade JC. Trichosporonosis in patients with neoplastic disease. *Medicine (Baltimore)* **1986**;65:268–79.
188. Patterson TF, Kirkpatrick WR, White M, et al. Invasive aspergillosis: disease spectrum, treatment practices, and outcomes. I3 Aspergillus Study Group. *Medicine (Baltimore)* **2000**;79:250–60.
189. Ascioglu S, Rex JH, de Pauw B, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin Infect Dis* **2002**;34:7–14.

190. Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systematic review of the literature. *Clin Infect Dis* **2001**; 32:358–66.
191. Kontoyiannis DP, Sumoza D, Tarrand J, Bodey GP, Storey R, Raad II. Significance of aspergillemia in patients with cancer: a 10-year study. *Clin Infect Dis* **2000**; 31:188–9.
192. Allo MD, Miller J, Townsend T, Tan C. Primary cutaneous aspergillosis associated with Hickman intravenous catheters. *N Engl J Med* **1987**; 317:1105–8.
193. Walmsley S, Devi S, King S, Schneider R, Richardson S, Ford-Jones L. Invasive *Aspergillus* infections in a pediatric hospital: a ten-year review. *Pediatr Infect Dis J* **1993**; 12:673–82.
194. Gartenberg G, Bottone EJ, Keusch GT, Weitzman I. Hospital-acquired mucormycosis (*Rhizopus rhizopodiformis*) of skin and subcutaneous tissue: epidemiology, mycology and treatment. *N Engl J Med* **1978**; 299:1115–8.
195. Dennis JE, Rhodes KH, Cooney DR, Roberts GD. Nosocomial *Rhizopus* infection (zygomycosis) in children. *J Pediatr* **1980**; 96:824–8.
196. Anaissie E. Opportunistic mycoses in the immunocompromised host: experience at a cancer center and review. *Clin Infect Dis* **1992**; 14(Suppl 1):S43–53.
197. Krcmery V Jr, Jesenska Z, Spanik S, et al. Fungaemia due to *Fusarium* spp. in cancer patients. *J Hosp Infect* **1997**; 36:223–8.
198. Boutati EI, Anaissie EJ. *Fusarium*, a significant emerging pathogen in patients with hematologic malignancy: ten years' experience at a cancer center and implications for management. *Blood* **1997**; 90:999–1008.
199. Sheehan DJ, Hitchcock CA, Sibley CM. Current and emerging azole antifungal agents. *Clin Microbiol Rev* **1999**; 12:40–79.
200. Wald A, Leisenring W, van Burik JA, Bowden RA. Epidemiology of *Aspergillus* infections in a large cohort of patients undergoing bone marrow transplantation. *J Infect Dis* **1997**; 175:1459–66.
201. Viscoli C, Girmenia C, Marinus A, et al. Candidemia in cancer patients: a prospective, multicenter surveillance study by the Invasive Fungal Infection Group (IFIG) of the European Organization for Research and Treatment of Cancer (EORTC). *Clin Infect Dis* **1999**; 28:1071–9.
202. Stevens DA, Kan VL, Judson MA, et al. Practice guidelines for diseases caused by *Aspergillus*. Infectious Diseases Society of America. *Clin Infect Dis* **2000**; 30:696–709.
203. Deresinski SC, Stevens DA. Caspofungin. *Clin Infect Dis* **2003**; 36:1445–57.
204. Wingard JR, Kubilis P, Lee L, et al. Clinical significance of nephrotoxicity in patients treated with amphotericin B for suspected or proven aspergillosis. *Clin Infect Dis* **1999**; 29:1402–7.
205. Walsh TJ, Hiemenz JW, Seibel NL, et al. Amphotericin B lipid complex for invasive fungal infections: analysis of safety and efficacy in 556 cases. *Clin Infect Dis* **1998**; 26:1383–96.
206. Walsh TJ, Finberg RW, Arndt C, et al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institute of Allergy and Infectious Diseases Mycoses Study Group. *N Engl J Med* **1999**; 340:764–71.
207. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* **2002**; 347:408–15.
208. Cagnoni PJ, Walsh TJ, Prendergast MM, et al. Pharmacoeconomic analysis of liposomal amphotericin B versus conventional amphotericin B in the empirical treatment of persistently febrile neutropenic patients. *J Clin Oncol* **2000**; 18:2476–83.
209. Marr KA, Seidel K, White TC, Bowden RA. Candidemia in allogeneic blood and marrow transplant recipients: evolution of risk factors after the adoption of prophylactic fluconazole. *J Infect Dis* **2000**; 181:309–16.
210. Ichiki Y, Hirose M, Akiyama T, Esaki C, Kitajima Y. Skin infection caused by *Mycobacterium avium*. *Br J Dermatol* **1997**; 136:260–3.
211. Sanderson TL, Moskowitz L, Hensley GT, Cleary TJ, Penneys N. Disseminated *Mycobacterium avium-intracellulare* infection appearing as a panniculitis. *Arch Pathol Lab Med* **1982**; 106:112–4.
212. Wallace RJ Jr, Brown BA, Onyi GO. Skin, soft tissue, and bone infections due to *Mycobacterium chelonae chelonae*: importance of prior corticosteroid therapy, frequency of disseminated infections, and resistance to oral antimicrobials other than clarithromycin. *J Infect Dis* **1992**; 166:405–12.
213. Bennett C, Vardiman J, Golomb H. Disseminated atypical mycobacterial infection in patients with hairy cell leukemia. *Am J Med* **1986**; 80:891–6.
214. Patel R, Roberts GD, Keating MR, Paya CV. Infections due to nontuberculous mycobacteria in kidney, heart, and liver transplant recipients. *Clin Infect Dis* **1994**; 19:263–73.
215. Gaviglia JM, Garcia PJ, Garrido SM, Corey L, Boeckh M. Nontuberculous mycobacterial infections in hematopoietic stem cell transplant recipients: characteristics of respiratory and catheter-related infections. *Biol Blood Marrow Transplant* **2000**; 6:361–9.
216. Berkey P, Bodey GP. Nocardial infection in patients with neoplastic disease. *Rev Infect Dis* **1989**; 11:407–12.
217. Simpson GL, Stinson EB, Egger MJ, Remington JS. Nocardial infections in the immunocompromised host: a detailed study in a defined population. *Rev Infect Dis* **1981**; 3:492–507.
218. Smego RA Jr, Moeller MB, Gallis HA. Trimethoprim-sulfamethoxazole therapy for *Nocardia* infections. *Arch Intern Med* **1983**; 143:711–8.
219. Dimino-Emme L, Gurevitch AW. Cutaneous manifestations of disseminated cryptococcosis. *J Am Acad Dermatol* **1995**; 32:844–50.
220. Neuville S, Dromer F, Morin O, Dupont B, Ronin O, Lortholary O. Primary cutaneous cryptococcosis: a distinct clinical entity. *Clin Infect Dis* **2003**; 36:337–47.
221. Anderson DJ, Schmidt C, Goodman J, Pomeroy C. Cryptococcal disease presenting as cellulitis. *Clin Infect Dis* **1992**; 14:666–72.
222. Saag MS, Graybill RJ, Larsen RA, et al. Practice guidelines for the management of cryptococcal disease. Infectious Diseases Society of America. *Clin Infect Dis* **2000**; 30:710–8.
223. Shuttleworth D, Philpot CM, Knight AG. Cutaneous cryptococcosis: treatment with oral fluconazole. *Br J Dermatol* **1989**; 120:683–7.
224. Davies SE, Sarosi GA, Peterson PK, et al. Disseminated histoplasmosis in renal transplant recipients. *Am J Surg* **1979**; 137:686–91.
225. Wheat J, Sarosi G, McKinsey D, et al. Practice guidelines for the management of patients with histoplasmosis. Infectious Diseases Society of America. *Clin Infect Dis* **2000**; 30:688–95.
226. Locksley RM, Flournoy N, Sullivan KM, Meyers JD. Infection with varicella-zoster virus after marrow transplantation. *J Infect Dis* **1985**; 152:1172–81.
227. Arvin AM, Pollard RB, Rasmussen LE, Merigan TC. Cellular and humoral immunity in the pathogenesis of recurrent herpes viral infections in patients with lymphoma. *J Clin Invest* **1980**; 65:869–78.
228. Balfour HH Jr, Bean B, Laskin OL, et al. Acyclovir halts progression of herpes zoster in immunocompromised patients. *N Engl J Med* **1983**; 308:1448–53.
229. Meyers JD, Flournoy N, Thomas ED. Infection with herpes simplex virus and cell-mediated immunity after marrow transplant. *J Infect Dis* **1980**; 142:338–46.
230. Tyring S, Barbarash RA, Nahlik JE, et al. Famciclovir for the treatment of acute herpes zoster: effects on acute disease and postherpetic neuralgia. A randomized, double-blind, placebo-controlled trial. Collaborative Famciclovir Herpes Zoster Study Group. *Ann Intern Med* **1995**; 123:89–96.
231. Cowan FM, Johnson AM, Ashley R, Corey L, Mindel A. Relationship between antibodies to herpes simplex virus (HSV) and symptoms of HSV infection. *J Infect Dis* **1996**; 174:470–5.
232. Johnson RE, Nahmias AJ, Magder LS, Lee FK, Brooks CA, Snowden CB. A seroepidemiologic survey of the prevalence of herpes simplex virus type 2 infection in the United States. *N Engl J Med* **1989**; 321:7–12.
233. Fleming DT, McQuillan GM, Johnson RE, et al. Herpes simplex virus type 2 in the United States, 1976 to 1994. *N Engl J Med* **1997**; 337:1105–11.

234. Balfour HH Jr, Benson C, Braun J, et al. Management of acyclovir-resistant herpes simplex and varicella-zoster virus infections. *J Acquir Immune Defic Syndr* **1994**;7:254–60.
235. Toome BK, Bowers KE, Scott GA. Diagnosis of cutaneous cytomegalovirus infection: a review and report of a case. *J Am Acad Dermatol* **1991**;24:860–7.
236. Mermel LA, Farr BM, Sherertz RJ, et al. Guidelines for the management of intravascular catheter-related infections. *Clin Infect Dis* **2001**;32:1249–72.

Note added in proof. Since this article was accepted for publication, the Food and Drug Administration has approved dalbavancin (Seltzer E, Dorr MB, Goldstein BP, et al. Once-weekly dalbavancin versus standard-of-care antimicrobial regimens for treatment of skin and soft-tissue infections. *Clin Infect Dis* 2003;37:1298–303) and tigecycline (Ellis-Grosse EJ, Babinchak T, Dartois N, et al. The efficacy and safety of tigecycline in the treatment of skin and skin-structure infections: results of 2 double-blind phase 3 comparison studies with vancomycin-aztreonam. *Clin Infect Dis* 2005;41[Suppl 5]:S341–53) for treatment of skin and soft-tissue infections, including those caused by methicillin-resistant *Staphylococcus aureus*. Dalbavancin was compared with the standard-of-care regimen, and cure rates and adverse effects were similar between study groups. Tigecycline was compared with vancomycin-aztreonam, and outcomes were similar between study groups. Interestingly, the incidence of nausea and vomiting was higher among patients in the tigecycline arm, and transaminase levels were higher in the vancomycin-aztreonam arm.