

Complicated infections of skin and skin structures: when the infection is more than skin deep

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Skin and skin-structure infections are common, and range from minor pyodermas to severe necrotizing infections. Complicated infections are defined as involving abnormal skin or wounds, occurring in compromised hosts, or requiring surgical intervention. Classification schemes for these infections are varied and confusing. Distinguishing characteristics include the aetiological agent(s), clinical context and findings, depth of tissue involvement and rate of progression. The most common pathogens are aerobic Gram-positive cocci, but complicated infections frequently involve Gram-negative bacilli and anaerobic bacteria. Initial antibiotic therapy is usually empirical, and later modified by the results of stains and cultures of wound specimens. Broad-spectrum coverage is frequently needed for complicated infections. Ertapenem is a once-a-day parenteral Group 1 carbapenem antibiotic, recently licensed in the USA and Europe, which may assume an important role in treating some complicated skin and skin-structure infections. Surgical debridement is important for many complicated infections, and is the critical element in managing necrotizing fasciitis and myonecrosis.

Keywords: cellulitis, necrotizing fasciitis, myonecrosis, gas gangrene

Introduction

Skin and skin structures are among the most frequent sites of human bacterial infection.^{1–5} They represent one of the most common indications for antibiotic therapy and account for ~10% of hospital admissions in the USA.⁶ Furthermore, the incidence of soft-tissue infections appears to be increasing, at least in some populations.⁶ Such infections are highly diverse in their aetiology, clinical manifestations and severity.^{1,2,7–10} Bacteria do not cause all skin infections, but this article will review only bacterial aetiologies. The pathogenesis of these infections usually involves direct inoculation of pathogens, but infection occasionally spreads to the skin contiguously from deeper foci^{11–13} or haematogenously from distant sites. Severity ranges from minor superficial lesions to invasive, fulminant and even lethal infections.

Classification of soft-tissue infections

The terminology used for infections of skin and skin structures is often confusing. Primary skin infections occur in otherwise normal skin and are usually caused by group A streptococci or *Staphylococcus aureus*. Secondary infections complicate chronic skin conditions (e.g. eczema or atopic dermatitis). These underlying disorders act as portals of entry for virulent bacteria. Other factors predisposing to skin infections include vascular insufficiency, disrupted venous

or lymphatic drainage, sensory neuropathies, diabetes mellitus, previous cellulitis, the presence of a foreign body, accidental or surgical trauma, obesity, poor hygiene and certain immunodeficiencies.¹⁰

A second level of classification divides skin and skin-structure infections into uncomplicated or complicated, the latter defined as involving abnormal skin or wounds, occurring in a compromised host, or requiring substantial surgical intervention.¹⁴ These infections are often further characterized as being acute (present for days to at most a few weeks) or chronic (persisting for many weeks to months). Soft-tissue infections can be localized or focal (e.g. impetigo, abscess) or diffuse (e.g. cellulitis, fasciitis). A clinically useful distinction with important management implications subdivides soft-tissue infections into non-necrotizing and necrotizing processes.¹ The key to treating serious infections successfully is prompt recognition, followed by appropriate antibiotic and, when needed, surgical therapy.

Specific infections of skin and skin structures can be grouped according to causative organism(s), the soft tissues involved (related to specific layers or depth of invasion) or the clinical syndrome (setting and presentation).¹ Other relevant issues include the epidemiology,^{5,15–17} pathogenesis^{4,18} and prognosis of the infection.¹⁹ Most proposed organizational schemata are cumbersome and difficult to remember or apply. We believe that a clinically useful system should be based on easily obtainable demographic, historical, physical

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Table 1. Classification of skin and skin-structure infections

Uncomplicated infections
superficial: impetigo, ecthyma
deeper: erysipelas, cellulitis
hair follicle associated: folliculitis, furunculosis
abscess: carbuncle, other cutaneous abscesses
Complicated infections
secondary infections of diseased skin
acute wound infections
traumatic
bite-related
post-operative
chronic wound infections
diabetic foot infections
venous stasis ulcers
pressure sores
perianal cellulitis ± abscess
Necrotizing fasciitis
polymicrobial fasciitis (type I)
Fournier's gangrene
synergic necrotizing 'cellulitis' with fasciitis and myonecrosis
streptococcal gangrene (type II)
fasciitis due to <i>V. vulnificus</i> and other <i>Vibrio</i> species
Myonecrosis
crepitant myonecrosis
clostridial myonecrosis
traumatic gas gangrene
atraumatic gas gangrene
synergic necrotizing 'cellulitis' with fasciitis and myonecrosis
non-crepitant myonecrosis
streptococcal gangrene with myonecrosis
<i>A. hydrophila</i> myonecrosis

examination and laboratory information that allows diagnostically important and therapeutically useful distinctions (Table 1).²⁰ Appropriate categorization should assist the clinician in recognizing: (i) which patients need prompt surgical intervention; and (ii) what empirical antibiotic regimen is most appropriate.

A few caveats regarding the nosology of these infections may be helpful. Although some soft-tissue infections primarily affect deeper structures, most entities have cutaneous manifestations as part of their initial (or sometimes later) presentation. In many cases, the critical first step is to recognize that an apparent cellulitis is, in reality, a fasciitis or myositis, or a manifestation of an underlying osteomyelitis or visceral abscess.^{21–23} Anatomical boundaries are not necessarily respected by invasive pathogens.²⁴ For example, although group A streptococcal gangrene is often grouped with necrotizing fasciitis, the process can range from a rapidly progressive cellulitis with a predilection to involve lymphatic vessels to a frank non-crepitant myositis.^{19,25} Although muscle injury may be the direct consequence of infection, it can also result from a para-inflammatory process without bacterial invasion; in either case, oedema may lead to a serious compartment syndrome.

The likelihood that a wound will become infected is directly related to the size of the microbial inoculum and the virulence of the organism(s), and inversely related to local and systemic host resistance. An estimate of the incubation period and apparent rate of progression of the infection can be diagnostically useful. An incu-

bation period of <24 h after trauma or surgery is most consistent with infection caused by *Streptococcus pyogenes*, *Clostridium perfringens* or *Pasteurella multocida*.² Other pathogens that characteristically have a short incubation period, abrupt onset and rapid progression include *Aeromonas hydrophila* and *Vibrio vulnificus*.²⁶ On the other hand, wound infections caused by *S. aureus* and Enterobacteriaceae usually incubate for at least 48–72 h (often longer) before clinical manifestations become evident, and they tend to advance less quickly. Small inocula may be followed by an incubation period of longer than a week. Indurated erythema developing at the site of vaccinia inoculation more than a week after immunization is more probably due to a robust cell-mediated immune response than to a bacterial superinfection. Patients with devitalized tissue or immunological deficiencies are susceptible to infections with bacteria generally considered non-pathogenic for normal hosts (e.g. coagulase-negative staphylococci, diphtheroids or *Bacillus* species).^{27–30}

Cellulitis

Most routine cellulitis acquired in the community is caused by *S. pyogenes* and/or *S. aureus*.^{31–37} Cellulitis due to *S. aureus* is more likely to be bullous and associated with a concomitant skin wound. Group A (and less often groups B, C and G) β-haemolytic streptococci can cause particularly aggressive cellulitis.^{38–42} When the lymphatics are involved by *S. pyogenes*, the skin becomes tense and palpably thickened to produce a 'peau d'orange' feel and appearance. The resulting erysipelas has elevated, well demarcated and usually rapidly advancing borders. The extremities, face, breast and perianal area may be involved.⁴³ Patients often have prominent constitutional complaints, such as fever, chills and malaise, which may antedate local signs or symptoms.⁴² Acute febrile neutrophilic dermatosis ('Sweet's syndrome') may present as a facial cellulitis resembling erysipelas.⁴⁴

Recurrent cellulitis is predominantly due to group A and other β-haemolytic streptococci.^{38,40} Repeated bouts of lower-extremity cellulitis may follow saphenous venectomy or varicose vein stripping,^{40,45,46} recurrent cellulitis at other sites (e.g. the arm or breast) is frequently caused by impaired lymphatic drainage secondary to neoplasia, radiation therapy, surgery or prior infection.^{47–50} Patients with a persistent break in the cutaneous barrier also experience recurrent infections.⁵¹ A common factor predisposing to recurrent cellulitis is tinea pedis, which is present in about half of the reported cases involving the leg.^{5,52} After the acute infection is controlled, the primary dermatological condition must be addressed to prevent recurrences. Patients with diabetes mellitus, chronic renal failure on haemodialysis, or who use illicit parenteral drugs may develop recurrent staphylococcal skin infections. This problem has been linked to nasal carriage of *S. aureus* and eradicating carriage with topical or systemic antimicrobials may lower the incidence.^{53–56} Prophylactic or symptom-prompted, patient-initiated antibiotic therapy may reduce morbidity from recurrent pyodermal infections.^{57–60} Unusual pathogens can cause recurrent cellulitis in immunocompromised hosts, as illustrated by *Helicobacter cinaedi* in HIV-infected patients. Some patients suffering from repeated episodes of what appears to be cellulitis actually have a non-infectious inflammatory disease.^{61–67} Episodes of 'pseudoerysipelas' are particularly difficult to distinguish from infection, but may respond more quickly and consistently to anti-inflammatory than to antimicrobial therapy.⁶⁷ Lipodermatosclerosis can occasionally present repetitively as a tender red plaque on the lower leg above the medial malleolus in patients with venous insufficiency, mimicking recurrent infection.^{68,69}

Skin and skin-structure infections

Table 2. Aetiological bacteria of soft-tissue infections by risk factor and setting

Risk factor/setting	Expected bacterial pathogen(s)
Cat bite	<i>P. multocida</i> and other <i>Pasteurella</i> species
Dog bite	<i>P. multocida</i> , <i>Capnocytophaga canimorsus</i> , CDC group EF-4
Rat bite	<i>Spirillum minor</i> ^a
Shark bite	<i>V. carchariae</i>
Human bite	<i>Eikenella corrodens</i> , <i>Fusobacterium</i> , <i>Prevotella</i> , streptococci, etc.
Animal hides, carcasses	<i>B. anthracis</i> , <i>Francisella tularensis</i>
Injection drug use	<i>S. aureus</i> , <i>Clostridium</i> spp., <i>E. corrodens</i> , <i>S. pyogenes</i>
Hot tub or wading pool	<i>P. aeruginosa</i>
Body piercing	<i>S. aureus</i> , <i>S. pyogenes</i> , <i>P. aeruginosa</i> ^b , <i>Clostridium tetani</i>
Medicinal leeches	<i>A. hydrophila</i> , <i>Aeromonas sobria</i> , <i>Serratia marcescens</i> , <i>Vibrio fluvialis</i>
Salon foot baths	<i>Mycobacterium fortuitum</i>
Fresh water injury	<i>A. hydrophila</i>
Salt water injury	<i>V. vulnificus</i>
Soil contamination	<i>Nocardia braziliensis</i> , <i>Clostridium</i> spp.
Fishmonger	<i>E. rhusiopathiae</i> , <i>Streptococcus iniae</i>
Fish tank exposure	<i>Mycobacterium marinum</i>

^a*Streptobacillus moniliformis*, the other recognized cause of rat-bite fever, does not classically present with prominent cutaneous signs at the site of the bite.

^b*P. aeruginosa* infections have generally followed piercing of the ear cartilage, not the ear lobe, and may cause disfiguring auricular chondritis.

Haemophilus influenzae is responsible for a distinctive cellulitis, usually in young children, which typically presents with a purplish discolouration of the cheek.⁷⁰ It is frequently associated with bacteraemia or meningitis.^{70,71} This entity has markedly decreased in frequency since the introduction of the conjugate *H. influenzae* type b vaccine.^{72–74} Although uncommon, *Streptococcus pneumoniae* occasionally causes cellulitis, especially in patients with systemic lupus erythematosus and other collagen vascular diseases.^{75,76}

The aetiological agent responsible for cellulitis may be suggested by the specific clinical context (Table 2). *Erysipelothrix rhusiopathiae* is a pleomorphic Gram-positive bacillus responsible for a generally indolent cellulitis, most commonly involving fingers that come into contact with fresh fish.^{77,78} The erysipeloid lesion is characteristically painful, well demarcated, slightly raised, faintly violaceous and spreads peripherally. Fever and systemic symptoms are not common,⁷⁹ and untreated lesions often involute over a few weeks. Suggested antibiotic therapy is with penicillins, cephalosporins, clindamycin or ciprofloxacin; vancomycin should not be used.

Bacillus anthracis causes a focal necrotizing cellulitis in persons having contact with infected animals or contaminated animal products (e.g. hides, goat hair).^{17,80,81} Unfortunately, its use as an agent of bioterrorism has removed the epidemiological constraints of naturally occurring infection.^{82,83} A papule appears at the site less than a week after inoculation. Within 2 days, small vesicles containing few leucocytes but many large Gram-positive bacilli evolve and enlarge, then undergo necrosis to form a painless ulcer covered by a black eschar surrounded by extensive non-pitting oedema. Skin lesions resembling different stages of cutaneous anthrax include furuncles and carbuncles, ecthyma, orf, brown recluse spider bites, rickettsial tache noire and ulceroglandular infections (such as tularaemia).^{84,85} Presumptive laboratory identification is based on Gram-stained smears of fluid or scrapings from the lesion. Oral therapy with ciprofloxacin, doxycycline or amoxicillin for 1–2 weeks is adequate for most cases unless inhalational exposure is also suspected.⁸⁶

P. multocida and other *Pasteurella* species are Gram-negative coccobacilli found in the oral cavity of many animals.^{87,88} Bites, scratches or licking of open wounds by cats or dogs may result in cellulitis within hours to a few days.^{4,18,89} Tenosynovitis is the most frequent local complication of *Pasteurella* soft-tissue infection. Fever develops in a minority of cases and bacteraemia is uncommon.^{88,90} Penicillins are effective treatment, but first-generation cephalosporins are unreliable.⁸⁸ Broader-spectrum agents that provide more comprehensive coverage of the variety of aerobic and anaerobic organisms associated with bite wounds (e.g. oral amoxicillin–clavulanate or parenteral ampicillin–sulbactam) are often administered.^{4,10,91}

V. vulnificus typically causes a rapidly advancing cellulitis associated with haemorrhagic bullae in both healthy persons and compromised hosts.⁹² The process may begin as, or progress to, necrotizing fasciitis (see below).^{92,93} The history typically discloses recent exposure of a skin abrasion to warm brackish seawater. *V. vulnificus* infection can result in disseminated disease culminating in septic shock, with or without a cutaneous portal of entry, usually in persons with cirrhosis or iron overload syndromes.^{26,92} Fulminant disease may quickly follow ingestion of raw oysters or clams in patients with hepatic cirrhosis, even when the liver disease is well compensated.^{94–96} *Vibrio hollisae* soft-tissue infections mimic the clinical picture of *V. vulnificus*. Other *Vibrio* species also cause serious wound infections, including *Vibrio carchariae* following shark bites, *Vibrio alginolyticus* and *Vibrio damsela*. Prompt antibiotic therapy, ideally with doxycycline, and early surgical intervention are usually indicated.

Complicated skin infections

Clinical presentations

Simple pyodermas are the most common skin infections, but are generally easy to diagnose, involve a limited number of predictable

pathogens and respond well to oral antibiotics.³¹ Complicated infections (e.g. extensive cellulitis, perianal abscess, traumatic or surgical wound infections, and foot infections in diabetic patients) are both more severe and difficult to treat.^{2,10,14,97} Even when limb- or life-threatening, these infections may be indolent in their pace but inexorably progressive despite medical therapy. The aetiological microbes in complicated infections are predominantly *S. aureus* and streptococci, but often involve mixed Gram-positive and Gram-negative aerobic and anaerobic bacteria as well.^{7,98,99} Enteric Gram-negative bacilli and *P. aeruginosa* tend to be associated with nosocomially acquired infections as well as infections in compromised hosts and injection drug users.³²

Several clinical syndromes are recognizable.^{2,20,21} Crepitant cellulitis may complicate dirty community-acquired traumatic injuries as well as surgical wounds. Nosocomial cases have developed at indwelling catheter sites. Clostridial cellulitis is a superficial infection associated with less systemic toxicity than clostridial myonecrosis (gas gangrene; see section 'Clostridial myonecrosis'). The process is usually indolent and rarely life threatening. Pain is relatively mild, and the bullous and necrotic skin lesions of gas gangrene do not develop. Crepitus, however, is more prominent in clostridial cellulitis than in gas gangrene. Gram-stained smears of exudate or aspirates disclose abundant large Gram-positive bacilli with surprisingly few neutrophils, and *C. perfringens* is usually recovered from anaerobic cultures. The clinical picture of non-clostridial crepitant cellulitis resembles clostridial cellulitis but may be more aggressive; causative bacteria include combinations of facultative species (e.g. *Escherichia coli*, *Klebsiella*, various streptococci) and strict anaerobes (e.g. *Bacteroides*, *Peptostreptococcus*).

A focal but necrotizing infection, termed progressive bacterial synergic gangrene, presents ~1–2 weeks after surgery as a necrotic ulcer with an outer zone of violaceous erythema.^{1,2} The process is seen most often in peri-colostomy and other postoperative infections of the abdominal wall. Meleney's ulcer denotes a similar lesion associated with multiple fistulous tracts emerging at a distance from the infected wound. This process results from co-infection with a microaerophilic *Streptococcus* and either *S. aureus* or a Gram-negative bacillus. The involved area progressively enlarges in widening circles unless treated appropriately by both antibiotics and wide surgical excision of all infected tissue.¹⁰⁰ The differential diagnosis of these lesions includes pyoderma gangrenosum, which can develop at sites of trauma, such as a postoperative wound, and amoebic ulcers. Supervening myonecrosis or necrotizing fasciitis should be suspected if the patient develops ecchymoses, bullae, crepitus, wet gangrene or anaesthesia of the overlying skin, especially in conjunction with systemic toxicity or laboratory evidence of rhabdomyolysis or disseminated intravascular coagulation.^{20–22}

The syndrome of purpura fulminans^{101,102} may complicate sepsis caused by several different bacterial species, including meningococcaemia. The sharply margined purpuric lesions are typically symmetrical, often on the distal extremities,^{103–105} and evolve into bullae filled with serous fluid, and ultimately to cutaneous necrosis.¹⁰⁶ Skin changes probably result from disseminated intravascular coagulation or protein C deficiency.^{101,102,107} Ecthyma gangrenosum most frequently complicates *P. aeruginosa* bacteraemia, but has been associated with septicaemia due to *A. hydrophila* and other Gram-negative bacilli.^{108–110}

Antibiotic therapy

Empirical antibiotic regimens for complicated skin-structure infections should always include coverage for aerobic Gram-positive cocci, specifically staphylococci and streptococci, and often for anaerobes, including the *Bacteroides fragilis* group.^{7,98,99} Methicillin-resistant *S. aureus* and Gram-negative bacilli are found in some mixed infections, especially those that occur in the hospital.³² *P. aeruginosa* is an uncommon soft-tissue pathogen in the community, but can cause wound infection following fresh water exposure or piercing of the ear cartilage, hot-tub folliculitis, or deep foot infections after a puncture wound through a sports shoe.^{111–115} Other non-fermentative species (e.g. *Acinetobacter*) rarely cause skin infections. Gram-negative organisms and methicillin-resistant staphylococci assume greater importance in superinfections after multiple courses of antibiotics, and in infections associated with profound neutropenia or injection drug use.^{34,116–118} However, methicillin-resistant *S. aureus* (MRSA) has been increasingly recognized as a cause of sporadic and epidemic skin infections arising in the community in those patients with no other risk factors, most commonly in children and young adults.^{119–121} Community-acquired MRSA often harbour the novel type IV staphylococcal cassette chromosome (SCC)mec element, which typically does not confer resistance to antimicrobial drugs other than β -lactam antibiotics, and sometimes contains the Panton–Valentine virulence gene, which may be involved in the pathogenesis of necrotizing skin or lung infections.

Several antibiotic classes have been shown to be effective, alone or in combination, against complicated soft-tissue infections:¹²² penicillin– β -lactamase inhibitor combinations (e.g. ampicillin–sulbactam, piperacillin–tazobactam),^{123–125} cephalosporins of all generations (e.g. cefazolin, cefixime, cefoxitin),^{126–128} fluoroquinolones (e.g. levofloxacin, moxifloxacin, clinafloxacin),^{129–132} glycopeptides (e.g. vancomycin),¹³³ quinupristin/dalfopristin¹³⁴ and oxazolidinones (e.g. linezolid).¹³⁵ Clindamycin and metronidazole are often added to the regimen to cover anaerobes, depending on the clinical context and other antibiotics being used. Reported clinical response rates are typically ~80–90%, with similar microbiological eradication rates. New agents for treating these infections may be helpful because of growing antibiotic resistance and to enhance convenience.

The traditional carbapenems (e.g. imipenem and meropenem)¹³⁶ cover an exceptionally wide spectrum of aerobic and anaerobic pathogens, and have been found to be effective in complicated soft-tissue infections.^{137,138} However, these older Group 2 carbapenems may have a broader spectrum than needed for most skin and soft-tissue infections,¹³⁶ and require multiple daily doses. In contrast, ertapenem is a new Group 1 carbapenem antibiotic¹³⁶ that is given once a day and is active against aerobic and anaerobic organisms generally associated with community-acquired infections.^{85,139} Its spectrum is appropriate for many complicated skin and skin-structure infections. A large multicentre trial for this indication compared intravenous therapy with ertapenem (1 g once a day) with piperacillin–tazobactam (3.375 g every 6 h) in a randomized double-blind study of 540 adults.¹²⁵ The most common conditions were soft-tissue abscesses and diabetic lower extremity infections. Patients with necrotizing fasciitis and myonecrosis were excluded. Mean duration of antibiotic therapy was 9–10 days. Clinical cure rates exceeded 80% and were statistically equivalent for the two regimens. Response rates for the two treatment groups were similar when stratified by diagnosis and infection severity. The overall frequency and severity of drug-related adverse events were also comparable in both treatment groups. Thus,

Skin and skin-structure infections

Table 3. Distinguishing features of the major types of deep, diffuse, necrotizing soft-tissue infections requiring prompt surgical intervention

	Depth of involvement	Usual pathogens	Predisposing event	Incubation period	Rate of progression	Characteristic features
Polymicrobial necrotizing fasciitis (type I)	fascia and muscle	obligate and facultative anaerobes	wound	long (48–96 h)	hours to days	foul-smelling drainage
Streptococcal gangrene (necrotizing fasciitis type II)	skin, fascia, muscle	group A>C>G>B streptococci	minor cut or abrasion	short (6–48 h)	a few hours	distinct margins
Gas gangrene (clostridial myonecrosis)	muscle	traumatic: <i>C. perfringens</i> > <i>C. novyi</i> atraumatic: <i>C. septicum</i>	contaminated wound	short (6–48 h)	a few hours	extreme systemic toxicity
Non-clostridial myonecrosis	muscle and fascia	obligate and facultative anaerobes or <i>A. hydrophila</i>	wound	variable (12–96 h)	hours to days	soft-tissue gas when polymicrobial aetiology

ertapenem appears to offer an additional option for complicated skin and skin-structure infections likely to be caused by susceptible mixed flora.

Although the intravenous route has traditionally been used to initiate treatment for most complicated infections, oral antibiotics may be adequate under some circumstances.^{130–132,140–142} Typically such cases involve patients with mild-to-moderate infections for whom there are appropriate agents available that can be tolerated by the oral route. Increasingly, oral therapy has been substituted in a step-down approach from the initial parenteral therapy.^{89,123,124} Certain antibiotics reliably achieve essentially equivalent plasma concentrations when administered parenterally or orally (e.g. trimethoprim–sulfamethoxazole, metronidazole, doxycycline, linezolid and the fluoroquinolones). Other drugs (e.g. amoxicillin–clavulanate and clindamycin) are less bioavailable after oral administration at standard doses but may still achieve therapeutic levels. For patients who do not require intravenous access for other reasons, intramuscular therapy is another consideration. Ertapenem and ceftriaxone are characterized by a long half-life and little local pain or inflammation after intramuscular injection.¹⁴³ This route of administration is generally not well accepted by patients for more than a few injections. Intramuscular administration may be most beneficial for outpatients who need only a limited number of parenteral doses, or as a stopgap measure between the loss of intravenous access and the re-establishment of new access.¹⁴⁴

In a non-compromised host with a focal superficial abscess, incision and drainage alone (without antibiotic therapy) may be sufficient treatment. For most other skin and skin-structure infections, antibiotic therapy is needed. The optimal duration of treatment for these infections has not been well defined, but antibiotics should usually be continued for ~3 days after all systemic and most local signs and symptoms of infection have subsided. The total duration of therapy for uncomplicated infections rarely needs to be more than a week in a normal host. More severe infections, especially in a compromised patient, can require 3–4 weeks of therapy. Underlying osteomyelitis dictates an even longer duration of antibiotic treatment.

If *S. aureus* with methicillin resistance or decreased susceptibility to vancomycin becomes widespread in the community, the standard empirical approach to antibiotic therapy for serious community-acquired infections will need to be carefully rethought.^{145–147}

Necrotizing fasciitis

Necrotizing fasciitis is an uncommon life-threatening infection affecting subcutaneous tissue.^{116,148–150} Onset is often acute and the course can be rapid.¹⁵¹ The confusing nomenclature is based on the aetiological agent(s), clinical findings, type and level of tissue involved, and rate of progression (Table 3). The term encompasses two distinct bacteriological entities that share many pathological and clinical features.^{20,149} Type I necrotizing fasciitis is a polymicrobial infection caused by facultative bacteria, such as non-groupable streptococci and Enterobacteriaceae, along with strict anaerobes, frequently including *Bacteroides* and *Peptostreptococcus*.^{152,153} Obligate aerobic organisms, such as *P. aeruginosa*, are rarely involved, but occasional cases are caused exclusively by anaerobes. Type II necrotizing fasciitis, or streptococcal gangrene, is caused by group A (less often group B, C or G) streptococci, usually alone but sometimes in association with *S. aureus*. Surgical procedures are paramount in treating these infections; antibiotic therapy plays an important but secondary role.

Polymicrobial (type I) necrotizing fasciitis

Factors that predispose to type I necrotizing fasciitis include diabetes mellitus, morbid obesity, alcoholism and parenteral drug use. The most common sites of involvement are the legs, abdominal wall, perineal area, postoperative wounds and, in the newborn, the umbilical stump. The affected area is initially swollen, erythematous with indistinct margins, warm, shiny and exquisitely tender. The process evolves with sequential colour changes from red–purple to patches of blue–grey. Cutaneous bullae and frank gangrene ultimately develop. Soft-tissue gas is often detectable, and the central area may become

anaesthetic secondary to destruction of superficial sensory nerves. Cutaneous hypoaesthesia and prominent systemic toxicity may antedate the appearance of skin necrosis and indicate that the process is deeper than a superficial cellulitis. The infection dissects along the tissue plane just superficial to the deep fascia. Marked oedema may produce a compartment syndrome with secondary myonecrosis, requiring prompt decompression. Gram-stained smears of exudate usually reveal a mixture of Gram-positive and Gram-negative organisms. Specimens of pus and deep tissue should be cultured for aerobes and anaerobes; some of the pathogens may be recovered from blood cultures.

Fournier's gangrene. Fournier's gangrene refers to necrotizing fasciitis involving the male genital region. The process may be confined to the scrotum or extend to the perineum, penis, buttock and abdominal wall.¹⁵⁴ Predisposing factors include diabetes mellitus, local trauma, paraphimosis, periurethral extravasation of urine, perirectal or perianal infections, and genitourinary surgery.¹⁵⁵ The infection commonly begins as a cellulitis adjacent to the portal of entry. Scrotal oedema and crepitus quickly increase, and dark purple patches develop and rapidly progress to extensive scrotal gangrene. With prompt and appropriate treatment (including surgery, antibiotics and sometimes hyperbaric oxygen), the testicles can often be preserved and the scrotum will usually regenerate.¹⁵⁴⁻¹⁶⁰

Synergic necrotizing cellulitis. Synergic necrotizing cellulitis is a confusing misnomer for a distinctive clinical variant of necrotizing fasciitis with prominent direct involvement of muscle.²⁰ Most infections involve the lower extremities. The lesion begins as a clustered area of small ulcers draining foul-smelling 'dishwater' pus. Circumscribed areas of gangrene develop around the draining areas, while the intervening skin remains uninvolved despite underlying necrosis. Local pain and tenderness are marked; crepitus, systemic toxicity and bacteraemia are common.

Streptococcal gangrene (type II necrotizing fasciitis)

Streptococcal gangrene occurs after minor trauma or surgery, particularly in patients with diabetes or peripheral vascular disease.^{24,161-163} Groups B, C and G streptococci cause infections indistinguishable from the classic group A gangrene, and tend to affect diabetic patients.^{41,99} Necrotizing fasciitis caused by streptococci may be a prominent part of the 'toxic strep syndrome'.^{162,164-166} Even when *S. aureus* is isolated from necrotic tissue, it usually contributes little to the pathogenesis. Streptococcal gangrene can be confined to the dermis, but the fascia is often the major site of involvement and myonecrosis may be the dominant process.^{38,162,167} Startlingly fast progression of erythema with distinct borders, quickly followed by gangrene, is a hallmark of this infection.¹⁶⁸ Gram-stained smears of exudate usually reveal chains of Gram-positive cocci, sometimes with interspersed clusters of larger Gram-positive cocci, and blood cultures may yield streptococci. High-dose penicillin and/or clindamycin appear to be the treatment of choice.^{150,166,169-171} However, prompt and adequate debridement, often requiring repeated operative procedures, is essential.^{153,172,173}

Myonecrosis

Bacterial myonecrosis can be caused by a variety of organisms, some of which produce gas deep within the involved muscles.¹⁷⁴ Myonecrosis often coexists with wound infection and necrotizing

fasciitis. Clinical distinctions are usually based on the presence or absence of crepitus and the presumed identity of the causative organism.

Clostridial myonecrosis

Clostridial myonecrosis (gas gangrene) refers to a rapidly progressive, life-threatening, toxæmic infection of skeletal muscle caused by clostridial species (principally *C. perfringens*).¹⁷⁵ It usually occurs after deep trauma with gross contamination or, less often, surgery.^{176,177} Rare cases have occurred after minor trauma (e.g. parenteral injections)^{16,178-180} Despite the high frequency of clostridial contamination of open wounds, the low incidence of gas gangrene attests to the prerequisite for devitalized tissue or foreign bodies in the pathogenesis of this infection. *Clostridium* species have been recovered from wounds and blood cultures in patients without evidence of infection due to these organisms.^{181,182}

Atraumatic gas gangrene designates clostridial myonecrosis developing in the absence of an obvious external insult. 'Spontaneous' myonecrosis is most often caused by haematogenous spread of *Clostridium septicum* from a colonic lesion, which is commonly occult and frequently malignant.¹⁸³ Diverticulitis, ischaemic bowel and neutropenic enterocolitis are other recognized underlying conditions. A few patients with spontaneous gas gangrene have multiple discrete sites of infection related to bacteraemic seeding.

The usual incubation period between injury and the onset of clostridial myonecrosis is 2-3 days, but may be as short as 6 h.¹⁷⁵ Typically the onset is alarmingly sudden, with pain out of proportion to the inciting injury. Cutaneous signs soon become apparent and the patient appears toxæmic. Brownish foul-smelling drainage, containing numerous organisms but few leucocytes, exudes from the wound. Gas bubbles may be visible in the discharge and deep crepitus is usually present, although generally not prominent. Tense blebs containing serosanguineous fluid develop in skin overlying necrotic muscle. Radiographs of involved areas reveal characteristic gaseous dissection of muscle and fascial planes. At surgery, infected muscle may initially exhibit only pallor, oedema and loss of elasticity, but rapidly becomes frankly necrotic. In the earliest stages, prior to its discolouration and dissolution, non-viable muscle may be identified by its lack of bleeding and failure to contract on stimulation.

Gram-stained smears of wound exudate or a bleb aspirate reveal only a few neutrophils but many large Gram-positive bacilli with blunt ends. *C. perfringens* is the most common isolate, followed in frequency by *Clostridium novyi* and *C. septicum*.¹⁸⁴ *E. coli*, other enteric Gram-negative bacilli and enterococci are sometimes recovered, reflecting the contaminated nature of the initiating lesion.¹⁵² *C. perfringens* may produce gas in anaerobic broth within 6 h of inoculation, providing an early presumptive identification of the infecting species.

The approach to suspected gas gangrene includes urgent surgical exploration to define the nature and extent of the process, to obtain specimens for stains and cultures, and to carry out appropriate debridement. Prompt, extensive, and often repeated, surgery is the principal treatment. All involved muscle, regardless of its gross appearance, should be resected so that the margins contain healthy bleeding tissue. Liberal fasciotomies to drain and decompress swollen fascial compartments may be necessary; unfortunately, limb amputation is sometimes required. Antibiotic therapy has traditionally consisted of high-dose intravenous penicillin. Currently, clindamycin (600 mg intravenously every 6-8 h) is often added to penicillin on the basis that the combination of penicillin with clindamycin has

Skin and skin-structure infections

been shown to provide greater efficacy than either agent alone in a murine model of gas gangrene.^{175,185–190}

Ancillary therapy for gas gangrene includes fluid and electrolyte replacement and often blood transfusions. The efficacy of hyperbaric oxygen therapy has not been conclusively established, but it may have an important role early in the treatment of seriously ill patients or in those with extensive involvement of the trunk in whom definitive surgical excision would be impossible or excessively mutilating.^{176,191–201} The usefulness of intravenously administered polyvalent antitoxin has not been demonstrated in this setting.^{175,202}

Non-clostridial myonecrosis

Non-clostridial myonecrosis encompasses at least four relatively distinct entities that differ from gas gangrene in their pathogenesis, clinical features and bacteriology: streptococcal myositis ± type II fasciitis (see earlier discussion under ‘Necrotizing fasciitis’); synergic necrotizing ‘cellulitis’ with type I fasciitis and myonecrosis (see earlier discussion under ‘Necrotizing fasciitis’); *A. hydrophila* myonecrosis; and superinfected dry gangrene. The last entity is a focal, usually indolent and primarily ischaemic process in the small muscles of a distal lower extremity already gangrenous from arterial insufficiency. Diabetic patients are prone to develop this complication, which usually does not extend beyond the area of vascular gangrene to involve viable muscle.

Rapidly progressive myonecrosis resembling clostridial gangrene but caused by *Aeromonas* species (usually *A. hydrophila*) may occur after injuries sustained (or contaminated) in a freshwater environment, or in conjunction with medicinal leech therapy.^{165,203,204} Lymphoma and leukaemia are predisposing factors in some cases.¹¹⁷ Cellulitis often develops within 12–48 h, accompanied by excruciating pain, marked oedema and bullae, serosanguineous drainage and systemic toxicity. Bacteraemia is frequently documented. Treatment requires prompt antimicrobial therapy and wide surgical debridement. Most isolates of *Aeromonas* are susceptible *in vitro* to gentamicin, trimethoprim–sulfamethoxazole, ciprofloxacin and third- or fourth-generation cephalosporins.

General observations on diagnosis and management

Initial management

The first and economically most important decision in treating skin infections concerns the need for hospitalization. Most pyoderms and uncomplicated soft-tissue infections do not require hospitalization. Complicated infections often require admission, especially if muscle or fascial involvement is suspected, the process is rapidly progressing, signs of toxæmia are developing, the diagnosis or prognosis is in doubt, exploratory surgery is contemplated or the patient cannot adequately comply with outpatient treatment. At the time of admission, the physician should carefully delineate and record the apparent extent of infection and consider whether or not surgical consultation or further diagnostic measures (see section ‘Diagnostic tests’) are indicated. Concurrently, any necessary supportive care should be initiated and an empirical antimicrobial regimen selected. Watchful waiting for 24–48 h on antibiotics to assess the clinical response to medical therapy may be appropriate in stable hospitalized patients. Local signs of cellulitis may initially worsen after starting therapy, but then should gradually improve. Rapidly advancing erythema or unremitting toxæmia should precipitate more aggressive evaluation. These patients must be reassessed regularly and frequently (preferably by the same clinician) during the first few hours and days

after admission.¹⁶¹ Many patients with cellulitis can be discharged in less than a day by using outpatient antimicrobial therapy.²⁰⁵

Diagnostic tests

Basic haematological studies and serum chemistries are appropriate for seriously ill patients. Leucocytosis (white blood cell count > 15 400/mm³) or hyponatraemia (serum sodium < 135 meq/L) increases the likelihood that necrotizing fasciitis is present in a patient with a severe soft-tissue infection.²¹ The utility of diagnostic aspiration of cellulitic skin is debated because of its low yield in identifying pathogens by stain or culture.^{206,207} When performed, aspirating near the advancing border of erythema or the point of maximal inflammation is usually advocated to increase the yield.²⁰⁸ On occasion, a Gram-stained smear of an appropriate wound specimen may provide rapid guidance to the causative organisms.⁷ A positive Gram-stained smear can be highly predictive of culture results when adequate samples from the site of infection can be obtained and properly processed. The presence of abundant neutrophils usually indicates the adequacy of the sample, but some histolytic bacteria, such as *C. perfringens*, destroy inflammatory cells at the site of infection. White cells also adhere to cotton-tipped swabs used to culture exudate, which dry quickly and absorb the specimen. For many complicated infections, a culture may provide useful information in selecting appropriate therapy; tissue specimens or aspirates are generally preferred to wound swabs. Blood cultures may be informative in those patients with systemic signs and symptoms, but their cost-effectiveness is low in uncomplicated patients with routine cellulites.^{209,210} In a study of adults with cellulitis, the probability of a contaminant (3.6%) exceeded that of a true pathogen (2.0%).²⁰⁹

Other diagnostic tests can supply important information in difficult or confusing cases. Soft-tissue radiographs may demonstrate a foreign body or gas in deep tissues.²¹¹ Computerized tomography or magnetic resonance imaging sometimes assist in defining the depth and extent of the process when the diagnosis of fasciitis or myonecrosis is in doubt.^{175,211} Often, surgical exploration is the most prudent diagnostic approach for seriously ill patients in whom the window of opportunity may be narrow.²¹²

Medical treatment

Antibiotic therapy. The clinical setting, apparent severity of the infection and the results of available laboratory tests should largely guide the choice of an antibiotic regimen. Initial empirical therapy of cellulitis should almost invariably cover aerobic Gram-positive cocci. The clinical course, epidemiological clues, local antibiotic susceptibility trends and/or microscopic examination of appropriate specimens may dictate broader coverage. Definitive therapy should ultimately be based on culture and susceptibility results as well as the clinical response to empirical therapy.

Ancillary measures. Simple measures such as elevation or compression of an oedematous²¹³ or inflamed extremity and therapy with non-steroidal anti-inflammatory drugs may hasten symptomatic resolution.^{214,215} Although non-steroidal drugs have been implicated in accelerating the progression of streptococcal gangrene and other forms of necrotizing fasciitis,^{216–220} the weight of evidence suggests that the putative association simply reflects masking of serious signs and symptoms by these anti-inflammatory agents,^{221–224} delaying accurate diagnosis and appropriate management.¹⁶⁷ Glucocorticoids may accelerate healing and reduce long-term relapse rates in patients with

erysipelas.^{225,226} Hyperbaric oxygen appears to benefit some patients with necrotizing or anaerobic infections.^{17,158,160,179,194,195,227–231} However, use of hyperbaric oxygen should not delay the prompt institution of necessary antibiotic therapy and surgical debridement. Intravenous γ -globulin, antitoxins, granulocyte-stimulating factors and other growth factors may have roles in selected patients.^{166,202,232–238} Attention to fluid and electrolyte requirements as well as other metabolic parameters is an important aspect of supportive care. Optimizing control of hyperglycaemia in diabetic patients appears to be important.^{239–242} Blood transfusions may be needed to replace perioperative loss. Patients with extensive necrosis may benefit from management in a burn centre.²⁴³ The application of sterile maggots has been advocated for selected patients with massive swelling following debridement of necrotizing fasciitis involving the head and neck, as well as for infected diabetic foot ulcers.²⁴⁴ Vacuum-assisted wound closure devices have been advocated for some infected wounds, but compelling data are scarce.^{7,245,246} Ultrasound and electrical stimulation have been used to promote healing of chronic ischaemic wounds.^{247,248}

Surgical indications. Operative intervention is rarely needed for uncomplicated pyoderms or cellulitis, but is critical to the diagnosis and therapy of necrotizing fasciitis and myonecroses.¹⁵³ Prompt surgical exploration with histopathological examination,²¹³ extensive debridement of devitalized tissue and decompression of ischaemic compartments is widely advocated for patients with suspected deep tissue necrosis, especially if rapidly advancing or adjacent to the trunk.^{172,173} The timing and extent of debridement are often the most hotly debated management decisions at the bedside in patients with diffuse necrotizing infections. As a general rule, it is usually safer to err on the side of too early or too much surgery. Getting ahead of a rapidly advancing fasciitis or myonecrosis offers the only real chance of cure in many cases.

Transparency declarations

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References

1. Lewis, R. T. (1988). Soft tissue infections. *World Journal of Surgery* **22**, 146–51.
2. Nichols, R. L. & Florman, S. (2001). Clinical presentations of soft-tissue infections and surgical site infections. *Clinical Infectious Diseases* **33**, Suppl. 2, S84–93.
3. Rhody, C. (2000). Bacterial infections of the skin. *Primary Care* **27**, 459–73.
4. Goldstein, E. J. (1992). Bite wounds and infection. *Clinical Infectious Diseases* **14**, 633–8.
5. Bisno, A. L. (1984). Cutaneous infections: microbiologic and epidemiologic considerations. *American Journal of Medicine* **76**, 172–9.
6. Centers for Disease Control. (2001). Incidence of soft tissue infections: San Francisco General Hospital—1996–2000. *Morbidity and Mortality Weekly Report* **50**, 381–4.

7. Bowler, P. G., Duerden, B. I. & Armstrong, D. G. (2001). Wound microbiology and associated approaches to wound management. *Clinical Microbiology Reviews* **14**, 244–69.
8. Sharma, S. & Verma, K. K. (2001). Skin and soft tissue infection. *Indian Journal of Pediatrics* **68**, Suppl. 3, S46–50.
9. Trent, J. T., Federman, D. & Kirsner, R. S. (2001). Common bacterial skin infections. *Ostomy/Wound Management* **47**, 30–4.
10. Lipsky, B. A. (2002). Cellulitis, erysipelas, and necrotizing soft-tissue infections. *Best Practice of Medicine*. <http://www.bestpracticeofmedicine.com> (date last accessed December 2003).
11. Lodha, A., Wales, P. W., James, A. *et al.* (2003). Acute appendicitis with fulminant necrotizing fasciitis in a neonate. *Journal of Pediatric Surgery* **38**, E5–6.
12. Mahler, C. W., Boormeester, M. A. & Busch, O. R. (2003). Acute diverticulitis mimicking necrotizing fasciitis. *Journal of the American College of Surgeons* **197**, 517.
13. Francoque, S. M., Van Laer, C., Struyf, N. *et al.* (2001). Perforating oesophageal carcinoma presenting as necrotizing fasciitis of the neck. *European Journal of Gastroenterology and Hepatology* **13**, 1261–4.
14. Center for Drug Evaluation and Research (CDER). (1998). Uncomplicated and complicated skin and skin structure infections—developing antimicrobial drugs for treatment. Guidance for Industry. <http://www.fda.gov/cder/guidance/2566dft.pdf> (date last accessed December 2003).
15. Winthrop, K. L., Abrams, M., Yakrus, M. *et al.* (2002). An outbreak of mycobacterial furunculosis associated with footbaths at a nail salon. *New England Journal of Medicine* **346**, 1366–71.
16. Bangsberg, D. R., Rosen, J. I., Aragon, T. *et al.* (2002). Clostridial myonecrosis cluster among injection drug users: a molecular epidemiology investigation. *Archives of Internal Medicine* **162**, 517–22.
17. Centers for Disease Control. (2002). Update: cutaneous anthrax in a laboratory worker—Texas, 2002. *Morbidity and Mortality Weekly Report* **51**, 482.
18. Weil, H. P., Fischer-Brugge, U. & Koch, P. (2002). Potential hazard of wound licking. *New England Journal of Medicine* **346**, 1336.
19. Sharkawy, A., Low, D. E., Saginur, R. *et al.* (2002). Severe group A streptococcal soft-tissue infections in Ontario: 1992–1996. *Clinical Infectious Diseases* **34**, 454–60.
20. Dellinger, E. P. (1981). Severe necrotizing soft-tissue infections. Multiple disease entities requiring a common approach. *Journal of the American Medical Association* **246**, 1717–21.
21. Wall, D. B., Klein, S. R., Black, S. *et al.* (2000). A simple model to help distinguish necrotizing fasciitis from nonnecrotizing soft tissue infection. *Journal of the American College of Surgeons* **191**, 227–31.
22. Landowski, M. A. (2002). Necrotizing fasciitis: a diagnostic and management challenge. *Ostomy/Wound Management* **48**, 18–21.
23. Trent, J. T. & Kirsner, R. S. (2002). Diagnosing necrotizing fasciitis. *Advances in Skin Wound Care* **15**, 135–8.
24. Smolyakov, R., Riesenberger, K., Schlaeffer, F. *et al.* (2002). Streptococcal septic arthritis and necrotizing fasciitis in an intravenous drug user couple sharing needles. *Israel Medical Association Journal* **4**, 302–3.
25. Adams, E. M., Gudmundsson, S., Yocum, D. E. *et al.* (1985). Streptococcal myositis. *Archives of Internal Medicine* **145**, 1020–3.
26. Patel, V. J., Gardner, E. & Burton, C. S. (2002). *Vibrio vulnificus* septicemia and leg ulcer. *Journal of the American Academy of Dermatology* **46**, Suppl. 5, S144–5.
27. King, C. T. (1994). Sternal wound infection due to *Corynebacterium xerosis*. *Clinical Infectious Diseases* **19**, 1171–2.
28. Brook, I. (1989). Microbiology of postthoractomy sternal wound infection. *Journal of Clinical Microbiology* **27**, 806–7.
29. Dancer, S. J., McNair, D., Finn, P. *et al.* (2002). *Bacillus cereus* cellulitis from contaminated heroin. *Journal of Medical Microbiology* **51**, 278–81.
30. Meredith, F. T., Fowler, V. G., Gautier, M. *et al.* (1997). *Bacillus cereus* necrotizing cellulitis mimicking clostridial myonecrosis: case

Skin and skin-structure infections

report and review of the literature. *Scandinavian Journal of Infectious Diseases* **29**, 528–9.

31. Hook, E. W., III, Hooton, T. M., Horton, C. A. *et al.* (1986). Microbiologic evaluation of cutaneous cellulitis in adults. *Archives of Internal Medicine* **146**, 295–7.

32. Doern, G. V., Jones, R. N., Pfaller, M. A. *et al.* (1999). Bacterial pathogens isolated from patients with skin and soft tissue infections: frequency of occurrence and antimicrobial susceptibility patterns from the SENTRY Antimicrobial Surveillance Program (United States and Canada, 1997). SENTRY Study Group (North America). *Diagnostic Microbiology and Infectious Disease* **34**, 65–72.

33. Laube, S. & Farrell, A. M. (2002). Bacterial skin infections in the elderly: diagnosis and treatment. *Drugs and Aging* **19**, 331–42.

34. Manfredi, R., Calza, L. & Chiodo, F. (2002). Epidemiology and microbiology of cellulitis and bacterial soft tissue infection during HIV disease: a 10-year survey. *Journal of Cutaneous Pathology* **29**, 168–72.

35. Fluit, A. C., Schmitz, F. J. & Verhoef, J. (2001). Frequency of isolation of pathogens from bloodstream, nosocomial pneumonia, skin and soft tissue, and urinary tract infections occurring in European patients. *European Journal of Clinical Microbiology and Infectious Diseases* **20**, 188–91.

36. Chiller, K., Selkin, B. A. & Murakawa, G. J. (2001). Skin microflora and bacterial infections of the skin. *Journal of Investigative Dermatology. Symposium Proceedings* **6**, 170–4.

37. Sigurdsson, A. F. & Gudmundsson, S. (1989). The etiology of bacterial cellulitis as determined by fine-needle aspiration. *Scandinavian Journal of Infectious Diseases* **21**, 537–42.

38. Bisno, A. L. & Stevens, D. L. (1996). Streptococcal infections of skin and soft tissues. *New England Journal of Medicine* **334**, 240–5.

39. Lewthwaite, P., Parsons, H. K., Bates, C. J. *et al.* (2002). Group G streptococcal bacteraemia: an opportunistic infection associated with immune senescence. *Scandinavian Journal of Infectious Diseases* **34**, 83–7.

40. Baddour, L. M. & Bisno, A. L. (1985). Non-group A β -hemolytic streptococcal cellulitis. Association with venous and lymphatic compromise. *American Journal of Medicine* **79**, 155–9.

41. Riefler, J., III, Molavi, A., Schwartz, D. *et al.* (1988). Necrotizing fasciitis in adults due to group B streptococcus. Report of a case and review of the literature. *Archives of Internal Medicine* **148**, 727–9.

42. Barzilai, A. & Choen, H. A. (1998). Isolation of group A streptococci from children with perianal cellulitis and from their siblings. *Pediatric Infectious Disease Journal* **17**, 358–60.

43. Bisno, A. L., Cockerill, F. R., III & Bermudez, C. T. (2000). The initial outpatient–physician encounter in group A streptococcal necrotizing fasciitis. *Clinical Infectious Diseases* **31**, 607–8.

44. Morgan, K. W. & Callan, J. P. (2001). Sweet's syndrome in acute myelogenous leukemia presenting as periorbital cellulitis with an infiltrate of leukemic cells. *Journal of the American Academy of Dermatology* **45**, 590–5.

45. Turner, D. P., Nagra, R. S., Large, S. *et al.* (1995). Recurrent cellulitis following coronary bypass surgery. *Journal of Hospital Infection* **30**, 78–80.

46. Hurwitz, R. M. & Tisserand, M. E. (1985). Streptococcal cellulitis proved by skin biopsy in a coronary artery bypass graft patient. *Archives of Dermatology* **121**, 908–9.

47. Woo, P. C., Lum, P. N., Wong, S. S. *et al.* (2000). Cellulitis complicating lymphoedema. *European Journal of Clinical Microbiology and Infectious Diseases* **19**, 294–7.

48. Ellison, R. T., III & McGregor, J. A. (1987). Recurrent postcoital lower-extremity streptococcal erythroderma in women. Streptococcal-sex syndrome. *Journal of the American Medical Association* **257**, 3260–2.

49. Mertz, K. R., Baddour, L. M., Bell, J. L. *et al.* (1998). Breast cellulitis following breast conservation therapy: a novel complication of medical progress. *Clinical Infectious Diseases* **26**, 481–6.

50. Brewer, V. H., Hahn, K. A., Rohrbach, B. W. *et al.* (2000). Risk factor analysis for breast cellulitis complicating breast conservation therapy. *Clinical Infectious Diseases* **31**, 654–9.

51. Dupuy, A., Benchikhi, H., Roujeau, J. C. *et al.* (1999). Risk factors for erysipelas of the leg (cellulitis): case–control study. *British Medical Journal* **318**, 1591–4.

52. Baddour, L. M. & Bisno, A. L. (1984). Recurrent cellulitis after coronary bypass surgery. Association with superficial fungal infection in saphenous venectomy limbs. *Journal of the American Medical Association* **251**, 1049–52.

53. Boyce, J. M. (1996). Preventing staphylococcal infections by eradicating nasal carriage of *Staphylococcus aureus*: proceeding with caution. *Infection Control and Hospital Epidemiology* **17**, 775–9.

54. Perl, T. M., Cullen, J. J., Wenzel, R. P. *et al.* (2002). Intranasal mupirocin to prevent postoperative *Staphylococcus aureus* infections. *New England Journal of Medicine* **346**, 1871–7.

55. Cimochoowski, G. E., Harostock, M. D., Brown, R. *et al.* (2001). Intranasal mupirocin reduces sternal wound infection after open heart surgery in diabetics and nondiabetics. *Annals of Thoracic Surgery* **71**, 1572–8.

56. Ruef, C., Fanconi, S. & Nadal, D. (1996). Sternal wound infection after heart operations in pediatric patients associated with nasal carriage of *Staphylococcus aureus*. *Journal of Thoracic and Cardiovascular Surgery* **112**, 681–6.

57. Klempner, M. S. & Styrt, B. (1988). Prevention of recurrent staphylococcal skin infections with low-dose oral clindamycin therapy. *Journal of the American Medical Association* **260**, 2682–5.

58. Kremer, M., Zuckerman, R., Avraham, Z. *et al.* (1991). Long-term antimicrobial therapy in the prevention of recurrent soft-tissue infections. *Journal of Infection* **22**, 37–40.

59. Wang, J. H., Liu, Y. C., Cheng, D. L. *et al.* (1997). Role of benzathine penicillin G in prophylaxis for recurrent streptococcal cellulitis of the lower legs. *Clinical Infectious Diseases* **25**, 685–9.

60. Pauszek, M. E. (1991). Prophylaxis for recurrent cellulitis complicating venous and lymphatic insufficiency. *Indiana Medicine* **84**, 252–3.

61. Berlyne, G. M., Kwan, T., Li, J. *et al.* (1989). Oedema protein concentrations for differentiation of cellulitis and deep vein thrombosis. *Lancet* **ii**, 728–9.

62. Houston, D. S. & Curran, J. (2001). Charcot foot. *Orthopaedic Nursing* **20**, 11–15.

63. Phelps, R. G. & Shoji, T. (2001). Update on panniculitis. *Mount Sinai Journal of Medicine* **68**, 262–7.

64. Stein, M. E., Drumea, K., Abu-Rasmi, R. *et al.* (1997). Taxol-induced cellulitis after extravasation: a rarely reported event. *American Journal of Clinical Oncology* **20**, 540.

65. Foo, K. F., Tao, M. & Tan, E. H. (2002). Gastric carcinoma presenting with cellulitis-like cutaneous metastasis. *Singapore Medical Journal* **43**, 37–8.

66. Faber, J., Shroeder, L., Thill, M. P. *et al.* (2002). Clinical picture: carcinoma erysipeloides of the neck. *Lancet* **359**, 1025.

67. Edwards, E. A. (1963). Recurrent febrile episodes and lymphoedema. *Journal of the American Medical Association* **184**, 858–62.

68. Bruce, A. J., Bennett, D. D., Lohse, C. M. *et al.* (2002). Lipodermatosclerosis: review of cases evaluated at Mayo Clinic. *Journal of the American Academy of Dermatology* **46**, 187–92.

69. Demitsu, T., Okada, O., Yoneda, K. *et al.* (1999). Lipodermatosclerosis—report of three cases and review of the literature. *Dermatology* **199**, 271–3.

70. Stanley, T. V. & Jogose, M. (1991). *Haemophilus influenzae* type b cellulitis. *New Zealand Medical Journal* **104**, 334–6.

71. Sankrithi, U. M. & LiPuma, J. J. (1991). Clinically inapparent meningitis complicating periorbital cellulitis. *Pediatric Emergency Care* **7**, 28–9.

72. Ambati, B. K., Ambati, J., Azar, N. *et al.* (2000). Periorbital and orbital cellulitis before and after the advent of *Haemophilus influenzae* type B vaccination. *Ophthalmology* **107**, 1450–3.

73. Donahue, S. P. & Schwartz, G. (1998). Preseptal and orbital cellulitis in childhood. A changing microbiologic spectrum. *Ophthalmology* **105**, 1902–5.
74. Adams, W. G., Deaver, K. A., Cochi, S. L. *et al.* (1993). Decline of childhood *Haemophilus influenzae* type b (Hib) disease in the Hib vaccine era. *Journal of the American Medical Association* **269**, 221–6.
75. DiNubile, M. J., Albornoz, M. A., Stumacher, R. J. *et al.* (1991). Pneumococcal soft-tissue infections: possible association with connective tissue diseases. *Journal of Infectious Diseases* **163**, 897–900.
76. Patel, M., Ahrens, J. C., Moyer, D. V. *et al.* (1994). Pneumococcal soft-tissue infections: a problem deserving more recognition. *Clinical Infectious Diseases* **19**, 149–51.
77. Hillenbrand, F. K. M. (1953). Whale finger and seal finger: their relation to erysipeloid. *Lancet* **i**, 680–1.
78. Brooke, C. J. & Riley, T. V. (1999). *Erysipelothrix rhusiopathiae*: bacteriology, epidemiology and clinical manifestations of an occupational pathogen. *Journal of Medical Microbiology* **48**, 789–99.
79. Hill, D. C. & Ghassemian, J. N. (1997). Epidemiologic investigations of bioterrorism-related anthrax, New Jersey, 2001. *Emerging Infectious Diseases* **8**, 1048–55.
80. Swartz, M. N. (2002). Recognition and management of anthrax—an update. *New England Journal of Medicine* **345**, 1621–5.
81. Greene, C. M., Reefhuis, J., Tan, C. *et al.* (2002). Epidemiologic investigations of bioterrorism-related anthrax, New Jersey, 2001. *Emerging Infectious Diseases* **8**, 1048–55.
82. Brachman, P. S. (2002). Bioterrorism: an update with a focus on anthrax. *American Journal of Epidemiology* **155**, 981–7.
83. Inglesby, T. V., O'Toole, T., Henderson, D. A. *et al.* (2002). Anthrax as a biological weapon, 2002: updated recommendations for management. *Journal of the American Medical Association* **287**, 2236–52.
84. Claeys, L. G. & Matamoros, R. (2002). Anaerobic cellulitis as the result of *Clostridium perfringens*: a rare cause of vascular access graft infection. *Journal of Vascular Surgery* **35**, 1287–8.
85. Syrjala, H., Karvonen, J. & Salminen, A. (1984). Skin manifestations of tularemia: a study of 88 cases in northern Finland during 16 years (1967–1983). *Acta Dermato-Venereologica* **64**, 513–6.
86. Pelak, B. A., Bartizal, K., Woods, G. L. *et al.* (2002). Comparative *in vitro* activities of ertapenem against aerobic and facultative bacterial pathogens from patients with complicated skin and skin structure infections. *Diagnostic Microbiology and Infectious Disease* **43**, 129–33.
87. Arons, M. S., Fernando, L. & Polayes, I. M. (1982). *Pasteurella multocida*—the major cause of hand infections following domestic animal bites. *Journal of Hand Surgery* **7**, 47–52.
88. Weber, D. J., Wolfson, J. S., Swartz, M. N. *et al.* (1984). *Pasteurella multocida* infections. Report of 34 cases and review of the literature. *Medicine (Baltimore)* **63**, 133–54.
89. Hara, H., Ochiai, T., Morishima, T. *et al.* (2002). *Pasteurella canis* osteomyelitis and cutaneous abscess after a domestic dog bite. *Journal of the American Academy of Dermatology* **46**, Suppl. 5, S151–2.
90. von Eiff, C., Becker, K., Machka, K. *et al.* (2001). Nasal carriage as a source of *Staphylococcus aureus* bacteremia. Study Group. *New England Journal of Medicine* **344**, 11–6.
91. Talan, D. A., Citron, D. M., Abrahamian, F. M. *et al.* (1999). Bacteriologic analysis of infected dog and cat bites. *New England Journal of Medicine* **340**, 85–92.
92. Upton, A. & Taylor, S. (2002). *Vibrio vulnificus* necrotizing fasciitis and septicemia. *New Zealand Medical Journal* **115**, 108–9.
93. Joynt, G. M., Gomersall, C. D. & Lyon, D. J. (1999). Severe necrotizing fasciitis of the extremities caused by Vibrionaceae: experience of a Hong Kong tertiary hospital. *Hong Kong Medical Journal* **5**, 63–8.
94. Bonner, J. R., Coker, A. S., Berryman, C. R. *et al.* (1983). Spectrum of *Vibrio* infections in a Gulf Coast community. *Annals of Internal Medicine* **99**, 464–9.
95. Potasman, I., Paz, A. & Odeh, M. (2002). Infectious outbreaks associated with bivalve shellfish consumption: a worldwide perspective. *Clinical Infectious Diseases* **35**, 921–8.
96. Chen, Y., Satoh, T. & Tokunaga, O. (2002). *Vibrio vulnificus* infection in patients with liver disease: report of five autopsy cases. *Virchows Archiv* **441**, 88–92.
97. Lipsky, B. A. (2001). Diabetic foot infections: progress in a pedestrian problem. *Contemporary Surgery* **57**, Suppl., S7–19.
98. Gerding, D. N. (1995). Foot infections in diabetic patients: the role of anaerobes. *Clinical Infectious Diseases* **20**, Suppl. 2, S283–8.
99. Reyzelman, A. M., Lipsky, B. A., Hadi, S. A. *et al.* (1999). The increased prevalence of severe necrotizing infections caused by non-group A streptococci. *Journal of the American Podiatric Medical Association* **89**, 454–7.
100. Ovens, N. & Fairhurst, J. (2002). Management of a heavily exuding, painful wound with necrotising subcutaneous infection. *Journal of Wound Care* **11**, 25–7.
101. Fourrier, F., Lestavel, P., Chopin, C. *et al.* (1990). Meningococemia and purpura fulminans in adults: acute deficiencies of proteins C and S and early treatment with antithrombin III concentrates. *Intensive Care Medicine* **16**, 121–4.
102. Powars, D. R., Rogers, Z. R., Patch, M. J. *et al.* (1987). Purpura fulminans in meningococemia: association with acquired deficiencies of proteins C and S. *New England Journal of Medicine* **317**, 571–2.
103. Welchon, J. G., Armstrong, D. G. & Harkless, L. B. (1996). Pedal manifestations of meningococcal septicemia. *Journal of the American Podiatric Medical Association* **86**, 129–31.
104. Genoff, M. C., Hoffer, M. M., Achauer, B. *et al.* (1992). Extremity amputations in meningococemia-induced purpura fulminans. *Plastic and Reconstructive Surgery* **89**, 878–81.
105. Jacobsen, S. T. & Crawford, A. H. (1984). Amputation following meningococemia. A sequela to purpura fulminans. *Clinical Orthopaedics and Related Research* **185**, 214–9.
106. Gamber, G., Oschatz, E., Herkner, H. *et al.* (2001). Sepsis-associated purpura fulminans in adults. *Wiener Klinische Wochenschrift* **113**, 107–12.
107. Powars, D., Larsen, R., Johnson, J. *et al.* (1993). Epidemic meningococemia and purpura fulminans with induced protein C deficiency. *Clinical Infectious Diseases* **17**, 254–61.
108. Sevinsky, L. D., Viece, C., Ballesteros, D. O. *et al.* (1993). Ecthyma gangrenosum: a cutaneous manifestation of *Pseudomonas aeruginosa* sepsis. *Journal of the American Academy of Dermatology* **29**, 104–6.
109. Fergie, J. E., Patrick, C. C. & Lott, L. (1991). *Pseudomonas aeruginosa* cellulitis and ecthyma gangrenosum in immunocompromised children. *Pediatric Infectious Disease Journal* **10**, 496–500.
110. Del Pozo, J., Garcia-Silva, J., Almagro, M. *et al.* (1998). Ecthyma gangrenosum-like eruption associated with *Morganella morganii* infection. *British Journal of Dermatology* **139**, 520–1.
111. Agger, W. A. & Mardan, A. (1995). *Pseudomonas aeruginosa* infections of intact skin. *Clinical Infectious Diseases* **20**, 302–8.
112. Keene, W. E., Markum, A. C. & Samadpour, M. (2004). Outbreak of *Pseudomonas aeruginosa* infections caused by commercial piercing of upper ear cartilage. *Journal of the American Medical Association* **291**, 981–5.
113. Tweeten, S. S. M. & Rickman, L. S. (1998). Infectious complications of body piercing. *Clinical Infectious Diseases* **26**, 735–40.
114. Centers for Disease Control and Prevention. (2000). Pseudomonas dermatitis/folliculitis associated with pools and hot tubs—Colorado and Maine, 1999–2000. *Morbidity and Mortality Weekly Report* **49**, 1087–91.
115. Inaba, A. S., Zukin, D. D. & Perro, M. (1992). An update on the evaluation and management of plantar puncture wounds and *Pseudomonas osteomyelitis*. *Pediatric Emergency Care* **8**, 38–44.
116. Fustes-Morales, A., Gutierrez-Castrellon, P., Duran-Mckinster, C. *et al.* (2002). Necrotizing fasciitis: report of 39 pediatric cases. *Archives of Dermatology* **138**, 893–9.
117. Johnston, D. L., Waldhausen, J. H. & Park, J. R. (2001). Deep soft tissue infections in the neutropenic pediatric oncology patient. *Journal of Pediatric Hematology and Oncology* **23**, 443–7.

Skin and skin-structure infections

118. Summanen, P. H., Talan, D. A., Strong, C. *et al.* (1995). Bacteriology of skin and soft-tissue infections: comparison of infections in intravenous drug users and individuals with no history of intravenous drug use. *Clinical Infectious Diseases* **20**, Suppl. 2, S279–82.
119. Eady, E. A. & Cove, J. H. (2003). Staphylococcal resistance revisited: community-acquired methicillin resistant *Staphylococcus aureus*—an emerging problem for the management of skin and soft tissue infections. *Current Opinion in Infectious Diseases* **16**, 103–24.
120. Salgado, C. D., Farr, B. M. & Calfee, D. P. (2003). Community-acquired methicillin-resistant *Staphylococcus aureus*: a meta-analysis of prevalence and risk factors. *Clinical Infectious Diseases* **36**, 131–9.
121. Vandenesch, F., Naimi, T., Enright, M. C. *et al.* (2003). Community-acquired methicillin-resistant *Staphylococcus aureus* carrying the Pantone–Valentine leukocidin genes: worldwide emergence. *Emerging Infectious Diseases* **9**, 978–84.
122. Brook, I. (1993). Antimicrobial therapy of skin and soft tissue infection in children. *Journal of the American Podiatric Medical Association* **83**, 398–405.
123. Tan, J. S., Wishnow, R. M., Talan, D. A. *et al.* (1993). Treatment of hospitalized patients with complicated skin and skin structure infections: double-blind, randomized, multicenter study of piperacillin–tazobactam versus ticarcillin–clavulanate. The Piperacillin/Tazobactam Skin and Skin Structure Study Group. *Antimicrobial Agents and Chemotherapy* **37**, 1580–6.
124. Lipsky, B. A., Baker, P. D., Landon, G. C. *et al.* (1997). Antibiotic therapy for diabetic foot infections: comparison of two parenteral-to-oral regimens. *Clinical Infectious Diseases* **24**, 643–8.
125. Graham, D. R., Lucasti, C., Malafaia, O. *et al.* (2002). Ertapenem once daily versus piperacillin–tazobactam 4 times per day for treatment of complicated skin and skin-structure infections in adults: results of a prospective, randomized, double-blind multicenter study. *Clinical Infectious Diseases* **34**, 1460–8.
126. Lautre, G. & Baker, L. W. (1972). Cephalixin therapy of soft-tissue infection. *South African Medical Journal* **46**, 837–9.
127. Brown, G., Chamberlain, R., Goulding, J. *et al.* (1996). Ceftriaxone versus cefazolin with probenecid for severe skin and soft tissue infections. *Journal of Emergency Medicine* **14**, 547–51.
128. Grayson, M. L., McDonald, M., Gibson, K. *et al.* (2002). Once-daily intravenous cefazolin plus oral probenecid is equivalent to once-daily intravenous ceftriaxone plus oral placebo for the treatment of moderate-to-severe cellulitis in adults. *Clinical Infectious Diseases* **34**, 1440–8.
129. Siami, G., Christou, N., Eisman, I. *et al.* (2001). Clinafloxacin versus piperacillin–tazobactam in treatment of patients with severe skin and soft tissue infections. *Antimicrobial Agents and Chemotherapy* **45**, 525–31.
130. Graham, D. R., Talan, D. A., Nichols, R. L. *et al.* (2002). Once-daily, high-dose levofloxacin versus ticarcillin–clavulanate alone or followed by amoxicillin–clavulanate for complicated skin and skin-structure infections: a randomized, open-label trial. *Clinical Infectious Diseases* **35**, 381–9.
131. Gentry, L. O., Rodriguez-Gomez, G., Zeluff, B. J. *et al.* (1989). A comparative evaluation of oral ofloxacin versus intravenous cefotaxime therapy for serious skin and skin structure infections. *American Journal of Medicine* **87**, 57S–60S.
132. Gentry, L. O., Ramirez-Ronda, C. H., Rodriguez-Noriega, E. *et al.* (1989). Oral ciprofloxacin vs parenteral cefotaxime in the treatment of difficult skin and skin structure infections. A multicenter trial. *Archives of Internal Medicine* **149**, 2579–83.
133. Vinken, A., Li, Z., Balan, D. *et al.* (2001). Economic evaluation of linezolid, flucloxacillin and vancomycin in the empirical treatment of cellulitis in UK hospitals: a decision analytical model. *Journal of Hospital Infection* **49**, Suppl. A, S13–24.
134. Nichols, R. L., Graham, D. R., Barriere, S. L. *et al.* (1999). Treatment of hospitalized patients with complicated Gram-positive skin and skin structure infections: two randomized, multicentre studies of quinupristin/dalfopristin versus cefazolin, oxacillin or vancomycin. Synergic Skin and Skin Structure Infection Group. *Journal of Antimicrobial Chemotherapy* **44**, 263–73.
135. Stevens, D. L., Smith, L. G., Bruss, J. B. *et al.* (2000). Randomized comparison of linezolid (PNU-100766) versus oxacillin–dicloxacillin for treatment of complicated skin and soft tissue infections. *Antimicrobial Agents and Chemotherapy* **44**, 3408–13.
136. Shah, P. M. & Isaacs, R. D. (2003). Ertapenem, the first of a new group of carbapenems. *Journal of Antimicrobial Chemotherapy* **52**, 538–43.
137. Fass, R. J., Freimer, E. H. & McCloskey, R. V. (1985). Treatment of skin and soft tissue infections with imipenem/cilastatin. *American Journal of Medicine* **78**, 110–2.
138. Nichols, R. L., Smith, J. W., Geckler, R. W. *et al.* (1995). Meropenem versus imipenem/cilastatin in the treatment of hospitalized patients with skin and soft tissue infections. *Southern Medical Journal* **88**, 397–404.
139. Goldstein, E. J., Citron, D. M., Merriam, C. V. *et al.* (2001). Comparative *in vitro* activity of ertapenem and 11 other antimicrobial agents against aerobic and anaerobic pathogens isolated from skin and soft tissue animal and human bite wound infections. *Journal of Antimicrobial Chemotherapy* **48**, 641–51.
140. Chow, A. T., Chen, A., Lattime, H. *et al.* (2002). Penetration of levofloxacin into skin tissue after oral administration of multiple 750 mg once-daily doses. *Journal of Clinical Pharmacy and Therapeutics* **27**, 143–50.
141. Nicodemo, A. C., Robledo, J. A., Jasovich, A. *et al.* (1998). A multicentre, double-blind, randomised study comparing the efficacy and safety of oral levofloxacin versus ciprofloxacin in the treatment of uncomplicated skin and skin structure infections. *International Journal of Clinical Practice* **52**, 69–74.
142. Lipsky, B. A., Pecoraro, R. E., Larson, S. A. *et al.* (1990). Out-patient management of uncomplicated lower-extremity infections in diabetic patients. *Archives of Internal Medicine* **150**, 790–7.
143. Legua, P., Lema, J., Moll, J. *et al.* (2002). Safety and local tolerability of intramuscularly administered ertapenem diluted in lidocaine: a prospective, randomized, double-blind study versus intramuscular ceftriaxone. *Clinical Therapeutics* **24**, 434–44.
144. Nathwani, D. (2001). The management of skin and soft tissue infections: outpatient parenteral antibiotic therapy in the United Kingdom. *Chemotherapy* **47**, Suppl. 1, 17–23.
145. Martinez-Aguilar, G., Hammerman, W. A., Mason, E. O., Jr *et al.* (2003). Clindamycin treatment of invasive infections caused by community-acquired, methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* in children. *Pediatric Infectious Disease Journal* **22**, 593–8.
146. Stevens, D. L. (2003). Community-acquired *Staphylococcus aureus* infections: increasing virulence and emerging methicillin resistance in the new millennium. *Current Opinion in Infectious Diseases* **16**, 189–91.
147. Naimi, T. S., LeDell, K. H., Como-Sabetti, K. *et al.* (2003). Comparison of community- and health care-associated methicillin-resistant *Staphylococcus aureus* infection. *Journal of the American Medical Association* **290**, 2976–84.
148. Ghanem, A. N., Halim, I. A., Embil, J. M. *et al.* (2002). Necrotizing fasciitis. *Saudi Medical Journal* **23**, 608–10.
149. Childers, B. J., Potyondy, L. D., Nachreiner, R. *et al.* (2002). Necrotizing fasciitis: a fourteen-year retrospective study of 163 consecutive patients. *American Surgery* **68**, 109–16.
150. Seal, D. V. (2001). Necrotizing fasciitis. *Current Opinion in Infectious Diseases* **14**, 127–32.
151. Hoeffel, J. C. & Hoeffel, F. (2002). Necrotizing fasciitis and purpura fulminans. *Plastic and Reconstructive Surgery* **109**, 2165.
152. Brook, I. & Frazier, E. H. (1998). Aerobic and anaerobic microbiology of infection after trauma. *American Journal of Emergency Medicine* **16**, 585–91.
153. Brandt, M. M., Corpron, C. A. & Wahl, W. L. (2000). Necrotizing soft tissue infections: a surgical disease. *American Surgery* **66**, 967–70.

154. Villanueva-Saenz, E., Martinez Hernandez-Magro, P., Valdes, O. M. *et al.* (2002). Experience in management of Fournier's gangrene. *Techniques in Coloproctology* **6**, 5–13.
155. Hodgson, D. J., Peters, J. L. & Shah, P. J. (2002). Perineal necrotizing fasciitis with dilatation of Cowper's gland. *Journal of the Royal Society of Medicine* **95**, 136–7.
156. Hollabaugh, R. S., Jr, Dmochowski, R. R., Hickerson, W. L. *et al.* (1998). Fournier's gangrene: therapeutic impact of hyperbaric oxygen. *Plastic and Reconstructive Surgery* **101**, 94–100.
157. Korhonen, K., Hirn, M. & Niinikoski, J. (1998). Hyperbaric oxygen in the treatment of Fournier's gangrene. *European Journal of Surgery* **164**, 251–5.
158. Lucca, M., Unger, H. D. & Devenny, A. M. (1990). Treatment of Fournier's gangrene with adjunctive hyperbaric oxygen therapy. *American Journal of Emergency Medicine* **8**, 385–7.
159. Riegels-Nielsen, P., Hesselgeldt-Nielsen, J., Bang-Jensen, E. *et al.* (1984). Fournier's gangrene: 5 patients treated with hyperbaric oxygen. *Journal of Urology* **132**, 918–20.
160. Ziser, A., Girsh, Z., Gozal, D. *et al.* (1985). Hyperbaric oxygen therapy for Fournier's gangrene. *Critical Care Medicine* **13**, 773–4.
161. Yoder, E. L., Mendez, J. & Khatib, R. (1987). Spontaneous gangrenous myositis induced by *Streptococcus pyogenes*: case report and review of the literature. *Reviews of Infectious Diseases* **9**, 382–5.
162. Ben Abraham, R., Keller, N., Vered, R. *et al.* (2002). Invasive group A streptococcal infections in a large tertiary center: epidemiology, characteristics and outcome. *Infection* **30**, 81–5.
163. Francis, B. A., Mui, A. L. & Calonje, D. (2001). Orbital streptococcal gangrene and AIDS. *Orbit* **20**, 243–8.
164. Lang, M. E., Vaudry, W. & Robinson, J. L. (2003). Case report and literature review of late-onset group B streptococcal disease manifesting as necrotizing fasciitis in preterm infants: is this a new syndrome? *Clinical Infectious Diseases* **37**, e132–5.
165. Barnham, M. R., Weightman, N. C., Anderson, A. W. *et al.* (2002). Streptococcal toxic shock syndrome: a description of 14 cases from North Yorkshire, UK. *Clinical Microbiology and Infection* **8**, 174–81.
166. Shaaban, H., Bayat, A., Davenport, P. *et al.* (2002). Necrotizing fasciitis in an infant with congenital insensitivity to pain syndrome. *British Journal of Plastic Surgery* **55**, 160–3.
167. Diazgranados, C. & Bisno, A. (2001). Clues to early diagnosis of group A streptococcal necrotizing fasciitis. *Infections in Medicine* **18**, 198–206.
168. Chelsom, J., Halstensen, A., Haga, T. *et al.* (1994). Necrotizing fasciitis due to group A streptococci in western Norway: incidence and clinical features. *Lancet* **344**, 1111–5.
169. Stevens, D. L., Gibbons, A. E., Bergstrom, R. *et al.* (1988). The Eagle effect revisited: efficacy of clindamycin, erythromycin, and penicillin in the treatment of streptococcal myositis. *Journal of Infectious Diseases* **158**, 23–8.
170. Stevens, D. L. (2000). Streptococcal toxic shock syndrome associated with necrotizing fasciitis. *Annual Review of Medicine* **51**, 271–88.
171. Stevens, D. L., Madaras-Kelly, K. J. & Richards, D. M. (1998). In vitro antimicrobial effects of various combinations of penicillin and clindamycin against four strains of *Streptococcus pyogenes*. *Antimicrobial Agents and Chemotherapy* **42**, 1266–8.
172. Burge, T. S. (1995). Necrotizing fasciitis—the hazards of delay. *Journal of the Royal Society of Medicine* **88**, 342P–343P.
173. Bilton, B. D., Zibari, G. B., McMillan, R. W. *et al.* (1998). Aggressive surgical management of necrotizing fasciitis serves to decrease mortality: a retrospective study. *American Surgery* **64**, 397–400.
174. Qvist, G. (1941). Anaerobic cellulitis and gas gangrene. *British Medical Journal* **2**, 217.
175. Cline, K. A. & Turnbull, T. L. (1985). Clostridial myonecrosis. *Annals of Emergency Medicine* **14**, 459–66.
176. Johnson, J. T., Gillespie, T. E., Cole, J. R. *et al.* (1969). Hyperbaric oxygen therapy for gas gangrene in war wounds. *American Journal of Surgery* **118**, 839–43.
177. Meltzer, R. M., Engel, E. D. & Turf, R. (1983). Postoperative gas gangrene. *Journal of Foot Surgery* **22**, 126–33.
178. Van Hook, R. & Vandeveld, A. G. (1975). Gas gangrene after intramuscular injection of epinephrine: report of fatal case. *Annals of Internal Medicine* **83**, 669–70.
179. Kalani, M., Jorreskog, G., Naderi, N. *et al.* (2002). Hyperbaric oxygen (HBO) therapy in treatment of diabetic foot ulcers. Long-term follow-up. *Journal of Diabetes Complications* **16**, 153–8.
180. Parish, L. C., Routh, H. B., Miskin, B. *et al.* (2000). Moxifloxacin versus cephalexin in the treatment of uncomplicated skin infections. *International Journal of Clinical Practice* **54**, 497–503.
181. Gorbach, S. L. & Thadepalli, H. (1975). Isolation of *Clostridium* in human infections: evaluation of 114 cases. *Journal of Infectious Diseases* **131**, Suppl., S81–5.
182. Ramsay, A. M. (1949). The significance of *Clostridium welchii* in the cervical swab and blood-stream in postpartum and postabortion sepsis. *Journal of Obstetrics and Gynaecology* **56**, 247–8.
183. Jacob, Z. C., Dedekian, M. & Seoudi, H. (2002). Nontraumatic clostridial myonecrosis: an indication for colonoscopy? *American Surgery* **68**, 463–5.
184. Noone, M., Tabaqchali, M. & Spillane, J. B. (2002). *Clostridium novyi* causing necrotising fasciitis in an injecting drug user. *Journal of Clinical Pathology* **55**, 141–2.
185. Muhvich, K. H., Anderson, L. H. & Mehm, W. J. (1994). Evaluation of antimicrobials combined with hyperbaric oxygen in a mouse model of clostridial myonecrosis. *Journal of Trauma* **36**, 7–10.
186. Bodey, G. P., Rodriguez, S., Fainstein, V. *et al.* (1991). Clostridial bacteremia in cancer patients. A 12-year experience. *Cancer* **67**, 1928–42.
187. Traub, W. H. (1988). Chemotherapy of experimental (murine) *Clostridium perfringens* type A gas gangrene. *Chemotherapy* **34**, 472–7.
188. Stevens, D. L., Laine, B. M. & Mitten, J. E. (1987). Comparison of single and combination antimicrobial agents for prevention of experimental gas gangrene caused by *Clostridium perfringens*. *Antimicrobial Agents and Chemotherapy* **31**, 312–6.
189. Stevens, D. L., Maier, K. A. & Mitten, J. E. (1987). Effect of antibiotics on toxin production and viability of *Clostridium perfringens*. *Antimicrobial Agents and Chemotherapy* **31**, 213–8.
190. Stevens, D. L., Maier, K. A., Laine, B. M. *et al.* (1987). Comparison of clindamycin, rifampin, tetracycline, metronidazole, and penicillin for efficacy in prevention of experimental gas gangrene due to *Clostridium perfringens*. *Journal of Infectious Diseases* **155**, 220–8.
191. Korhonen, K., Klossner, J., Hirn, M. *et al.* (1999). Management of clostridial gas gangrene and the role of hyperbaric oxygen. *Annales chirurgiae et gynaecologiae* **88**, 139–42.
192. Stephens, M. B. (1996). Gas gangrene: potential for hyperbaric oxygen therapy. *Postgraduate Medicine* **99**, 217–24.
193. Hirn, M., Niinikoski, J. & Lehtonen, O. P. (1992). Effect of hyperbaric oxygen and surgery on experimental gas gangrene. *European Surgery Research* **24**, 356–62.
194. Trivedi, D. R. & Raut, V. V. (1990). Role of hyperbaric oxygen therapy in the rapid control of gas gangrene infection and its toxemia. *Journal of Postgraduate Medicine* **36**, 13–15.
195. Slack, W. K. (1976). Hyperbaric oxygen therapy in anaerobic infections: gas gangrene. *Proceedings of the Royal Society of Medicine* **69**, 326–7.
196. Larcen, A., Laprevote-Heully, M. C., Lambert, H. *et al.* (1974). Gas gangrene—on the basis of 19 observations. Advantages of combining surgery with hyperbaric oxygen therapy. *Materia Medica Polona* **6**, 116–9.
197. Schweigel, J. F. & Shim, S. S. (1973). A comparison of the treatment of gas gangrene with and without hyperbaric oxygen. *Surgery, Gynecology and Obstetrics* **136**, 969–70.
198. Maudsley, R. H. & Arden, G. P. (1972). Gas gangrene and hyperbaric oxygen. *British Medical Journal* **4**, 362.

Skin and skin-structure infections

199. Roding, B., Groeneveld, P. H. & Boerema, I. (1972). Ten years of experience in the treatment of gas gangrene with hyperbaric oxygen. *Surgery, Gynecology and Obstetrics* **134**, 579–85.
200. Slack, W. K., Hanson, G. C. & Chew, H. E. (1969). Hyperbaric oxygen in the treatment of gas gangrene and clostridial infection. A report of 40 patients treated in a single-person hyperbaric oxygen chamber. *British Journal of Surgery* **56**, 505–10.
201. Colwill, M. R. & Maudsley, R. H. (1968). The management of gas gangrene with hyperbaric oxygen therapy. *Journal of Bone and Joint Surgery. British volume* **50**, 732–42.
202. Hamsa, W. R. & Burney, D. W., Jr (1966). Gas gangrene infection: combined treatment including 3,432,000 international units of polyvalent gas gangrene antitoxin. *Nebraska State Medical Journal* **51**, 85–9.
203. Gold, W. L. & Salit, I. E. (1993). *Aeromonas hydrophila* infections of skin and soft tissue: report of 11 cases and review. *Clinical Infectious Diseases* **16**, 69–74.
204. Mackay, D. R., Manders, E. K., Siggers, G. C. *et al.* (1999). *Aeromonas* species isolated from medicinal leeches. *Annals of Plastic Surgery* **42**, 275–9.
205. Eron, L. J. & Passos, S. (2001). Early discharge of infected patients through appropriate antibiotic use. *Archives of Internal Medicine* **161**, 61–5.
206. Kielhofner, M. A., Brown, B & Dall, L. (1988). Influence of underlying disease process on the utility of cellulitis needle aspirates. *Archives of Internal Medicine* **148**, 2451–2.
207. Sachs, M. K. (1990). The optimum use of needle aspiration in the bacteriologic diagnosis of cellulitis in adults. *Archives of Internal Medicine* **150**, 1907–12. [Erratum, (1991). *Archives of Internal Medicine* **151**, 244]
208. Howe, P. M., Eduardo Fajardo, J. & Orcutt, M. A. (1987). Etiologic diagnosis of cellulitis: comparison of aspirates obtained from the leading edge and the point of maximal inflammation. *Pediatric Infectious Disease Journal* **6**, 685–6.
209. Perl, B., Gottehrer, N. P., Raveh, D. *et al.* (1999). Cost-effectiveness of blood cultures for adult patients with cellulitis. *Clinical Infectious Diseases* **29**, 1483–8.
210. Sadow, K. B. & Chamberlain, J. M. (1998). Blood cultures in the evaluation of children with cellulitis. *Pediatrics* **101**, E4.
211. Struk, D. W., Munk, P. L., Lee, M. J. *et al.* (2001). Imaging of soft tissue infections. *Radiologic Clinics of North America* **39**, 277–303.
212. Stamenkovic, I. & Lew, P. D. (1984). Early recognition of potentially fatal necrotizing fasciitis. The use of frozen-section biopsy. *New England Journal of Medicine* **310**, 1689–93.
213. Armstrong, D. G. & Nguyen, H. C. (2000). Improvement in healing with aggressive edema reduction after debridement of foot infection in persons with diabetes. *Archives of Surgery* **135**, 1405–9.
214. Edmonds, M., Wilson, M. & Foster, A. (1999). Diabetic foot ulcers. *Nursing Standard* **14**, 39–45.
215. Cox, N. H. (2002). Management of lower leg cellulitis. *Clinical Medicine* **2**, 23–7.
216. Brun-Buisson, C. J., Saada, M., Trunet, P. *et al.* (1985). Haemolytic streptococcal gangrene and non-steroidal antiinflammatory drugs. *British Medical Journal (Clinical Research Edition)* **290**, 1786.
217. Choo, P. W., Donahue, J. G. & Platt, R. (1997). Ibuprofen and skin and soft tissue superinfections in children with varicella. *Annals of Epidemiology* **7**, 440–5.
218. Forbes, N. & Rankin, A. P. (2001). Necrotizing fasciitis and non-steroidal antiinflammatory drugs: a case series and review of the literature. *New Zealand Medical Journal* **114**, 3–6.
219. Guibal, F., Muffat-Joly, M., Terris, B. *et al.* (1998). Effects of diclofenac on experimental streptococcal necrotizing fasciitis (NF) in rabbit. *Archives in Dermatological Research* **290**, 628–33.
220. Kaul, R., McGeer, A., Low, D. E. *et al.* (1997). Population-based surveillance for group A streptococcal necrotizing fasciitis: clinical features, prognostic indicators, and microbiologic analysis of seventy-seven cases. Ontario Group A Streptococcal Study. *American Journal of Medicine* **103**, 18–24.
221. Barnham, M. (1997). Nonsteroidal antiinflammatory drugs: concurrent or causative drugs in serious infection? *Clinical Infectious Diseases* **25**, 1272–3.
222. Barnham, M. & Anderson, A. W. (1997). Non-steroidal anti-inflammatory drugs (NSAIDs). A predisposing factor for streptococcal bacteraemia? *Advances in Experimental Medicine and Biology* **418**, 145–7.
223. Stevens, D. L. (1995). Could nonsteroidal antiinflammatory drugs (NSAIDs) enhance the progression of bacterial infections to toxic shock syndrome? *Clinical Infectious Diseases* **21**, 977–80.
224. Aronoff, D. M. & Bloch, K. C. (2003). Assessing the relationship between the use of nonsteroidal antiinflammatory drugs and necrotizing fasciitis caused by Group A *Streptococcus*. *Medicine* **82**, 225–35.
225. Bergkvist, P. I. & Sjobeck, K. (1997). Antibiotic and prednisolone therapy of erysipelas: a randomized, double blind, placebo-controlled study. *Scandinavian Journal of Infectious Diseases* **29**, 377–82.
226. Bergkvist, P. I. & Sjobeck, K. (1998). Relapse of erysipelas following treatment with prednisolone or placebo in addition to antibiotics: a 1-year follow-up. *Scandinavian Journal of Infectious Diseases* **30**, 206–7.
227. Baroni, G., Porro, T., Faglia, E. *et al.* (1987). Hyperbaric oxygen in diabetic gangrene treatment. *Diabetes Care* **10**, 81–6.
228. Eitorai, I. M., Hart, G. B., Strauss, M. B. *et al.* (1986). The role of hyperbaric oxygen in the management of Fournier's gangrene. *International Surgery* **71**, 53–8.
229. McDonald, D. F., Hulet, W. H. & Cowan, J. W. (1975). Scrotal gangrene treated with oxygen under high pressure. *Journal of Urology* **113**, 364–6.
230. Yuen, J. C. & Feng, Z. (2002). Salvage of limb and function in necrotizing fasciitis of the hand: role of hyperbaric oxygen treatment and free muscle flap coverage. *Southern Medical Journal* **95**, 255–7.
231. Ulkur, E., Yuksel, F., Acikel, C. *et al.* (2002). Effect of hyperbaric oxygen on pedicle flaps with compromised circulation. *Microsurgery* **22**, 16–20.
232. Owen-Smith, M. S. (1968). Antibiotics and antitoxin therapy in the prophylaxis of experimental gas gangrene. *British Journal of Surgery* **55**, 43–5.
233. Shemanova, G. F., Vlasova, E. V. & Postnikova, T. M. (1988). On the *in vitro* neutralization test of *Clostridium perfringens* type A toxin. *Journal of Hygiene, Epidemiology, Microbiology, and Immunology* **32**, 219–26.
234. Jude, E. B., Blakytyn, R., Bulmer, J. *et al.* (2002). Transforming growth factor- β 1, 2, 3 and receptor type I and II in diabetic foot ulcers. *Diabetic Medicine* **19**, 440–7.
235. Shackelford, D. P., Fackler, E., Hoffman, M. K. *et al.* (2002). Use of topical recombinant human platelet-derived growth factor BB in abdominal wound separation. *American Journal of Obstetrics and Gynecology* **186**, 701–4.
236. Fu, X., Shen, Z., Guo, Z. *et al.* (2002). Healing of chronic cutaneous wounds by topical treatment with basic fibroblast growth factor. *Chinese Medical Journal (Engl)* **115**, 331–5.
237. Mann, A., Breuhahn, K., Schirmacher, P. *et al.* (2001). Keratinocyte-derived granulocyte-macrophage colony stimulating factor accelerates wound healing: stimulation of keratinocyte proliferation, granulation tissue formation, and vascularization. *Journal of Investigative Dermatology* **117**, 1382–90.
238. Rumalla, V. K. & Borah, G. L. (2001). Cytokines, growth factors, and plastic surgery. *Plastic and Reconstructive Surgery* **108**, 719–33.
239. Golden, S. H., Peart-Vigilance, C., Kao, W. H. *et al.* (1999). Perioperative glycemic control and the risk of infectious complications in a cohort of adults with diabetes. *Diabetes Care* **22**, 1408–14.
240. Pomposelli, J. J., Baxter, J. K., III, Babineau, T. J. *et al.* (1998). Early postoperative glucose control predicts nosocomial infection rate in diabetic patients. *Journal of Parenteral and Enteral Nutrition* **22**, 77–81.
241. Van den Berge, G. (2002). Intensive insulin therapy in critically ill patients. *New England Journal of Medicine* **345**, 1359–67.
242. Furnary, A. P., Zerr, K. J., Grunkemeier, G. L. *et al.* (1999). Continuous intravenous insulin infusion reduces the incidence of deep

M. J. DiNubile and B. A. Lipsky

sternal wound infection in diabetic patients after cardiac surgical procedures. *Annals of Thoracic Surgery* **67**, 352–60.

243. Faucher, L. D., Morris, S. E., Edelman, L. S. *et al.* (2001). Burn center management of necrotizing soft-tissue surgical infections in unburned patients. *American Journal of Surgery* **182**, 563–9.

244. Dunn, C., Raghavan, U. & Pfeleiderer, A. G. (2002). The use of maggots in head and neck necrotizing fasciitis. *Journal of Laryngology and Otology* **116**, 70–2.

245. Armstrong, D. G., Lavery, L. A., Abu-Rumman, P. *et al.* (2002). Outcomes of subatmospheric pressure dressing therapy on wounds of the diabetic foot. *Ostomy/Wound Management* **48**, 64–8.

246. Ford, C. N., Reinhard, E. R., Yeh, D. *et al.* (2002). Interim analysis of a prospective, randomized trial of vacuum-assisted closure versus the healthpoint system in the management of pressure ulcers. *Annals of Plastic Surgery* **49**, 55–61.

247 Gardner, S. E. , Frantz, R. A. & Schmidt, F. L. (1999). Effect of electrical stimulation on chronic wound healing: a meta-analysis. *Wound Repair Regeneration* **7**, 495–503.

248 Peters, E. J., Lavery, L. A., Armstrong, D. J. *et al.* (2001). Electric stimulation as an adjunct to heal diabetic foot ulcers: a randomized clinical trial. *Archives Physical and Medical Rehabilitation* **82**, 721–5.