

## 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.<sup>1–5</sup> They represent one of the most common indications for antibiotic therapy and account for ~10% of hospital admissions in the USA.<sup>6</sup> Furthermore, the incidence of soft-tissue infections appears to be increasing, at least in some populations.<sup>6</sup> Such infections are highly diverse in their aetiology, clinical manifestations and severity.<sup>1,2,7–10</sup> 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<sup>11–13</sup> 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.<sup>10</sup>

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.<sup>14</sup> 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.<sup>1</sup> 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).<sup>1</sup> Other relevant issues include the epidemiology,<sup>5,15–17</sup> pathogenesis<sup>4,18</sup> and prognosis of the infection.<sup>19</sup> 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).<sup>20</sup> 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.<sup>21–23</sup> Anatomical boundaries are not necessarily respected by invasive pathogens.<sup>24</sup> 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.<sup>19,25</sup> 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*.<sup>2</sup> Other pathogens that characteristically have a short incubation period, abrupt onset and rapid progression include *Aeromonas hydrophila* and *Vibrio vulnificus*.<sup>26</sup> 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).<sup>27–30</sup>

## Cellulitis

Most routine cellulitis acquired in the community is caused by *S. pyogenes* and/or *S. aureus*.<sup>31–37</sup> 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.<sup>38–42</sup> 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.<sup>43</sup> Patients often have prominent constitutional complaints, such as fever, chills and malaise, which may antedate local signs or symptoms.<sup>42</sup> Acute febrile neutrophilic dermatosis ('Sweet's syndrome') may present as a facial cellulitis resembling erysipelas.<sup>44</sup>

Recurrent cellulitis is predominantly due to group A and other β-haemolytic streptococci.<sup>38,40</sup> Repeated bouts of lower-extremity cellulitis may follow saphenous venectomy or varicose vein stripping,<sup>40,45,46</sup> 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.<sup>47–50</sup> Patients with a persistent break in the cutaneous barrier also experience recurrent infections.<sup>51</sup> A common factor predisposing to recurrent cellulitis is tinea pedis, which is present in about half of the reported cases involving the leg.<sup>5,52</sup> 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.<sup>53–56</sup> Prophylactic or symptom-prompted, patient-initiated antibiotic therapy may reduce morbidity from recurrent pyodermal infections.<sup>57–60</sup> 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.<sup>61–67</sup> Episodes of 'pseudoerysipelas' are particularly difficult to distinguish from infection, but may respond more quickly and consistently to anti-inflammatory than to antimicrobial therapy.<sup>67</sup> 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.<sup>68,69</sup>

## 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> <sup>a</sup>
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> <sup>b</sup> , <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>

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

<sup>b</sup>*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.<sup>70</sup> It is frequently associated with bacteraemia or meningitis.<sup>70,71</sup> This entity has markedly decreased in frequency since the introduction of the conjugate *H. influenzae* type b vaccine.<sup>72–74</sup> Although uncommon, *Streptococcus pneumoniae* occasionally causes cellulitis, especially in patients with systemic lupus erythematosus and other collagen vascular diseases.<sup>75,76</sup>

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.<sup>77,78</sup> The erysipeloid lesion is characteristically painful, well demarcated, slightly raised, faintly violaceous and spreads peripherally. Fever and systemic symptoms are not common,<sup>79</sup> 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).<sup>17,80,81</sup> Unfortunately, its use as an agent of bioterrorism has removed the epidemiological constraints of naturally occurring infection.<sup>82,83</sup> 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).<sup>84,85</sup> 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.<sup>86</sup>

*P. multocida* and other *Pasteurella* species are Gram-negative coccobacilli found in the oral cavity of many animals.<sup>87,88</sup> Bites, scratches or licking of open wounds by cats or dogs may result in cellulitis within hours to a few days.<sup>4,18,89</sup> Tenosynovitis is the most frequent local complication of *Pasteurella* soft-tissue infection. Fever develops in a minority of cases and bacteraemia is uncommon.<sup>88,90</sup> Penicillins are effective treatment, but first-generation cephalosporins are unreliable.<sup>88</sup> 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.<sup>4,10,91</sup>

*V. vulnificus* typically causes a rapidly advancing cellulitis associated with haemorrhagic bullae in both healthy persons and compromised hosts.<sup>92</sup> The process may begin as, or progress to, necrotizing fasciitis (see below).<sup>92,93</sup> 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.<sup>26,92</sup> Fulminant disease may quickly follow ingestion of raw oysters or clams in patients with hepatic cirrhosis, even when the liver disease is well compensated.<sup>94–96</sup> *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.<sup>31</sup> 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.<sup>2,10,14,97</sup> 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.<sup>7,98,99</sup> 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.<sup>32</sup>

Several clinical syndromes are recognizable.<sup>2,20,21</sup> 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.<sup>1,2</sup> 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.<sup>100</sup> 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.<sup>20–22</sup>

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

### 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.<sup>7,98,99</sup> Methicillin-resistant *S. aureus* and Gram-negative bacilli are found in some mixed infections, especially those that occur in the hospital.<sup>32</sup> *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.<sup>111–115</sup> 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.<sup>34,116–118</sup> 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.<sup>119–121</sup> 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  $\beta$ -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:<sup>122</sup> penicillin– $\beta$ -lactamase inhibitor combinations (e.g. ampicillin–sulbactam, piperacillin–tazobactam),<sup>123–125</sup> cephalosporins of all generations (e.g. cefazolin, cefixime, cefoxitin),<sup>126–128</sup> fluoroquinolones (e.g. levofloxacin, moxifloxacin, clinafloxacin),<sup>129–132</sup> glycopeptides (e.g. vancomycin),<sup>133</sup> quinupristin/dalfopristin<sup>134</sup> and oxazolidinones (e.g. linezolid).<sup>135</sup> 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)<sup>136</sup> cover an exceptionally wide spectrum of aerobic and anaerobic pathogens, and have been found to be effective in complicated soft-tissue infections.<sup>137,138</sup> However, these older Group 2 carbapenems may have a broader spectrum than needed for most skin and soft-tissue infections,<sup>136</sup> and require multiple daily doses. In contrast, ertapenem is a new Group 1 carbapenem antibiotic<sup>136</sup> that is given once a day and is active against aerobic and anaerobic organisms generally associated with community-acquired infections.<sup>85,139</sup> 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.<sup>125</sup> 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  gastrointestinal lesion, but no local insult	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.<sup>130–132,140–142</sup> 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.<sup>89,123,124</sup> 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.<sup>143</sup> 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.<sup>144</sup>

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.<sup>145–147</sup>

### Necrotizing fasciitis

Necrotizing fasciitis is an uncommon life-threatening infection affecting subcutaneous tissue.<sup>116,148–150</sup> Onset is often acute and the course can be rapid.<sup>151</sup> 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.<sup>20,149</sup> 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*.<sup>152,153</sup> 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.<sup>154</sup> Predisposing factors include diabetes mellitus, local trauma, paraphimosis, periurethral extravasation of urine, perirectal or perianal infections, and genitourinary surgery.<sup>155</sup> 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.<sup>154–160</sup>

**Synergic necrotizing cellulitis.** Synergic necrotizing cellulitis is a confusing misnomer for a distinctive clinical variant of necrotizing fasciitis with prominent direct involvement of muscle.<sup>20</sup> 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.<sup>24,161–163</sup> Groups B, C and G streptococci cause infections indistinguishable from the classic group A gangrene, and tend to affect diabetic patients.<sup>41,99</sup> Necrotizing fasciitis caused by streptococci may be a prominent part of the 'toxic strep syndrome'.<sup>162,164–166</sup> 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.<sup>38,162,167</sup> Startlingly fast progression of erythema with distinct borders, quickly followed by gangrene, is a hallmark of this infection.<sup>168</sup> 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.<sup>150,166,169–171</sup> However, prompt and adequate debridement, often requiring repeated operative procedures, is essential.<sup>153,172,173</sup>

### Myonecrosis

Bacterial myonecrosis can be caused by a variety of organisms, some of which produce gas deep within the involved muscles.<sup>174</sup> 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*).<sup>175</sup> It usually occurs after deep trauma with gross contamination or, less often, surgery.<sup>176,177</sup> Rare cases have occurred after minor trauma (e.g. parenteral injections).<sup>16,178–180</sup> 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.<sup>181,182</sup>

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.<sup>183</sup> 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.<sup>175</sup> 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*.<sup>184</sup> *E. coli*, other enteric Gram-negative bacilli and enterococci are sometimes recovered, reflecting the contaminated nature of the initiating lesion.<sup>152</sup> *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

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been shown to provide greater efficacy than either agent alone in a murine model of gas gangrene.<sup>175,185–190</sup>

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.<sup>176,191–201</sup> The usefulness of intravenously administered polyvalent antitoxin has not been demonstrated in this setting.<sup>175,202</sup>

### *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.<sup>165,203,204</sup> Lymphoma and leukaemia are predisposing factors in some cases.<sup>117</sup> 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 unrelenting 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.<sup>161</sup> Many patients with cellulitis can be discharged in less than a day by using outpatient antimicrobial therapy.<sup>205</sup>

### *Diagnostic tests*

Basic haematological studies and serum chemistries are appropriate for seriously ill patients. Leucocytosis (white blood cell count > 15 400/mm<sup>3</sup>) or hyponatraemia (serum sodium < 135 meq/L) increases the likelihood that necrotizing fasciitis is present in a patient with a severe soft-tissue infection.<sup>21</sup> The utility of diagnostic aspiration of cellulitic skin is debated because of its low yield in identifying pathogens by stain or culture.<sup>206,207</sup> When performed, aspirating near the advancing border of erythema or the point of maximal inflammation is usually advocated to increase the yield.<sup>208</sup> On occasion, a Gram-stained smear of an appropriate wound specimen may provide rapid guidance to the causative organisms.<sup>7</sup> 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.<sup>209,210</sup> In a study of adults with cellulitis, the probability of a contaminant (3.6%) exceeded that of a true pathogen (2.0%).<sup>209</sup>

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.<sup>211</sup> 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.<sup>175,211</sup> Often, surgical exploration is the most prudent diagnostic approach for seriously ill patients in whom the window of opportunity may be narrow.<sup>212</sup>

### *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 oedematous<sup>213</sup> or inflamed extremity and therapy with non-steroidal anti-inflammatory drugs may hasten symptomatic resolution.<sup>214,215</sup> Although non-steroidal drugs have been implicated in accelerating the progression of streptococcal gangrene and other forms of necrotizing fasciitis,<sup>216–220</sup> the weight of evidence suggests that the putative association simply reflects masking of serious signs and symptoms by these anti-inflammatory agents,<sup>221–224</sup> delaying accurate diagnosis and appropriate management.<sup>167</sup> Glucocorticoids may accelerate healing and reduce long-term relapse rates in patients with

erysipelas.<sup>225,226</sup> Hyperbaric oxygen appears to benefit some patients with necrotizing or anaerobic infections.<sup>17,158,160,179,194,195,227–231</sup> However, use of hyperbaric oxygen should not delay the prompt institution of necessary antibiotic therapy and surgical debridement. Intravenous  $\gamma$ -globulin, antitoxins, granulocyte-stimulating factors and other growth factors may have roles in selected patients.<sup>166,202,232–238</sup> 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.<sup>239–242</sup> Blood transfusions may be needed to replace perioperative loss. Patients with extensive necrosis may benefit from management in a burn centre.<sup>243</sup> 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.<sup>244</sup> Vacuum-assisted wound closure devices have been advocated for some infected wounds, but compelling data are scarce.<sup>7,245,246</sup> Ultrasound and electrical stimulation have been used to promote healing of chronic ischaemic wounds.<sup>247,248</sup>

**Surgical indications.** Operative intervention is rarely needed for uncomplicated pyoderma or cellulitis, but is critical to the diagnosis and therapy of necrotizing fasciitis and myonecrosis.<sup>153</sup> Prompt surgical exploration with histopathological examination,<sup>213</sup> 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.<sup>172,173</sup> 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

B.A.L. has received fees for speaking at symposia organized on behalf of Merck & Co., Inc., and Pharmacia, and has also received funds for research from Merck & Co., Inc., Pharmacia and Wyeth-Ayerst. B.A.L. is also a member of advisory boards for Merck & Co., Inc., Pharmacia, Wyeth-Ayerst, Cubist and Vicuron. M.J.D. is an employee of Merck & Co., Inc., and potentially owns stock and/or holds stock options in the Company.

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