SUPPLEMENT ARTICLE

Clinical Presentations of Soft-Tissue Infections and Surgical Site Infections

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Skin and soft-tissue infections that usually follow minor traumatic events or surgical procedures are caused by a wide spectrum of bacteria. Less frequently, the infections occur spontaneously, which often is clinically confusing and leads to delays in diagnosis. Most of the infections are self-limited and easily treated with local measures and/or antibiotics. Others are life-threatening, requiring prompt diagnosis and aggressive surgical debridement in addition to the wise choice of antibiotic agents to limit tissue loss and preserve life. Many survivors experience critical tissue losses that may require changes in lifestyle as well as major reconstructive cosmetic surgery. Involvement of antibiotic-resistant gram-positive microorganisms in these infections only increases the difficulty of their treatment and may have a significant influence on the ultimate outcome.

Skin and soft-tissue infections are frequently the cause for visits to health care providers. Most of these infections are superficial and readily treated with regimens of local care and antibiotics. However, others—for example, group A β-hemolytic streptococcal gangrene and clostridial myonecrosis—are life-threatening and require a combined medical and surgical intervention. Postoperative surgical site infections (SSIs) remain a major source of morbidity and a less frequent cause of mortality in surgical patients [1]. These infections average ~500,000/year among an estimated 27 million surgical procedures [2]. They account for approximately one-quarter of the estimated 2 million nosocomial infections that occur yearly [3]. Their development directly results in an increased duration of hospitalization and related medical expenses.

CLINICAL PRESENTATION OF SKIN AND SOFT-TISSUE INFECTIONS

The spectrum of bacterial diseases of the skin ranges from superficial, localized, easily recognized and easily treated skin eruptions to deep, aggressive, gangrenous, and necrotizing infections that might seem innocuous at first but quickly become life-threatening. Prompt recognition and treatment is paramount in limiting the morbidity and mortality associated with these infections. Physicians should demonstrate a healthy respect for the aggressiveness of gangrenous and necrotizing infections of the skin and soft tissues by harboring a high index of suspicion to increase the likelihood of early recognition and the administration of appropriate treatment before overwhelming clinical infection occurs.

Common Skin and Soft-Tissue Infections

Impetigo. Impetigo is the most common bacterial infection of the skin. It is highly contagious and can occur at any age, from infancy to adulthood, but it is most commonly seen in preschool-aged children. There are two classic forms of impetigo, nonbullous and bullous. Both forms have a predominantly staphylococcal etiology, although they present with different morphological characteristics.

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Nonbullous (crusted) impetigo can be recognized by the development of a serous, yellow-brown exudate, which dries into a golden crust. Lesions rarely elicit pain but can be associated with erythema and pruritus. They are most common on exposed areas, such as the hands, feet, and legs, and are often associated with a traumatic event, such as an insect bite or laceration. Crusted impetigo is usually associated with a heavy mixed flora of both staphylococci and streptococci. The bullous variety usually presents as a rapidly spreading papule, which may progress to a thin-walled vesicle if the lesion is infected with *Staphylococcus aureus,* an organism that produces an exfoliative toxin. These lesions are most common in warm, moist areas of the body. Predisposing factors include warm ambient temperatures, humidity, poor hygiene, and crowded living conditions.

Treatment of impetigo begins with eradication of the environmental factors thought to be influential in the development of the process. Aggressive lesion debridement with mesh gauze sponges or brushes and antibacterial soap is encouraged, as is special attention to hygiene, including disinfection of towels and bedding. Topical antibiotic treatment with mupirocin (Bactroban) has been effective in mild to moderate cases. However, there are increasing reports of mupirocin resistance. In more extensive cases, oral systemic antibiotic therapy with a penicillinase-resistant synthetic penicillin, such as oxacillin or dicloxacillin, is the treatment of choice. Erythromycin should not be used in communities that have a high incidence of resistant staphylococcal strains. Patients should be treated for at least 7 days. If no improvement is seen, lesions should be cultured and antibiotics adjusted appropriately.

Systemic complications from impetigo are very uncommon. Cellulitis can occur but is usually susceptible to systemic antibiotic therapy. Septicemia and staphylococcal scalded skin syndrome are exceedingly rare complications of impetigo, and when they occur, systemic therapy is indicated.

Folliculitis. Folliculitis is a pyoderma that arises within a hair follicle. When this infection extends beyond the hair follicle, the process is known as a "furuncle" or "boil." These lesions occur most frequently in the moist areas of the body and in areas subject to friction and perspiration. Host factors known to predispose to folliculitis include obesity, blood dyscrasias, defects in neutrophil function, and immune deficiency states (such as diabetes, transplant-related immunosuppression, and acquired immunodeficiency syndrome). The incidence is also higher among patients receiving treatment with corticosteroids or cytotoxic agents. The causative organism in most immunocompetent patients is *S. aureus;* however, when immunosuppression impairs host defenses, gram-negative organisms (*Klebsiella, Enterobacter,* and *Proteus* species) can be involved.

Successful treatment of folliculitis depends on correction of the predisposing factors that promote the development of this condition. For patients with localized disease, topical wound care, including an antibiotic such as mupirocin, is effective. Patients with furunculosis or multiple lesions should be treated with orally administered antibiotics that are effective against *S. aureus.* Any fluctuant nodules or masses should be incised and drained, and recurrent disease requires extended treatment.

Cellulitis. Cellulitis is an acute infection of the skin and underlying soft tissues. It commonly begins as a hot, red, edematous, sharply defined eruption and may progress to lymphangitis, lymphadenitis, and in severe cases, necrotizing fasciitis and gangrene. Cellulitis usually occurs in the setting of local skin trauma from insect bites, abrasions, surgical wounds, contusions, and other cutaneous lacerations. Immunosuppressed patients are particularly susceptible to the progression of cellulitis from regional to systemic infections, and these patients should receive aggressive treatment with parenteral antibiotics, drainage, and debridement when appropriate.

Initial presentation is that of a rapidly expanding, tender, erythematous, firm area of skin. An ascending lymphangitis may be present, especially in cellulitis of an extremity. Regional lymphadenopathy is common. Systemic signs and symptoms can eventually evolve and, when present, mandate hospitalization and treatment with systemic antibiotics. Offending organisms are most commonly group A β-hemolytic *Streptococcus* species and *S. aureus.*

If treatment of the uncomplicated localized processes caused by susceptible organisms requires intervention with antibiotics, oral agents, such as penicillinase-resistant penicillins or cephalosporins, could be used. If fever, septicemia, or other signs of advancement of the localized process to deeper tissues are present, the patient should be admitted to the hospital for blood

Figure 1. Streptococcal gangrenous infection (so-called flesh-eater) of the arm, involving skin and subcutaneous tissues, that followed a minor penetrating traumatic event.

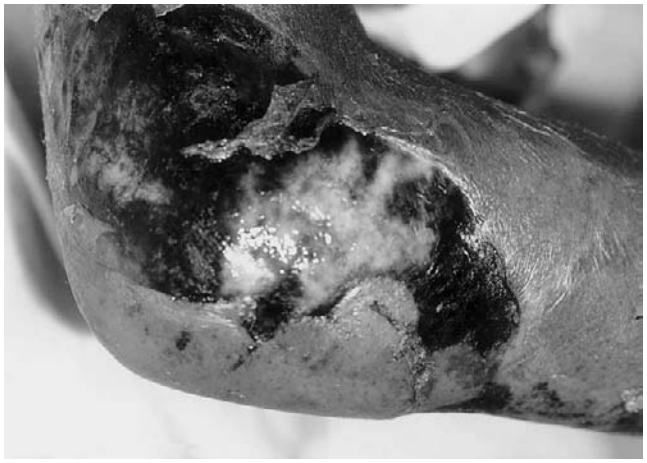

Figure 2. Close-up of the elbow of the patient shown in figure 1, displaying obvious necrosis of superficial tissues.

and wound cultures and for parenteral antibiotics. If a prompt response is not noted after parenteral antibiotic treatment has been administered, surgical exploration of the involved area may be indicated to rule out the presence of deeper necrotic or gangrenous tissue.

Abscess. Classic signs and symptoms, such as pain (dolor), redness (rubor), heat (calor), and swelling (tumor), indicate inflammation, which is usually due to bacterial infection. Loss of function associated with fluctuance indicates abscess formation. Localization of purulent fluid necessitates surgical drainage and local wound care. Oral or parenteral antibiotic therapy should be administered when indicated clinically after results of wound cultures and susceptibilities of organisms are determined.

Life-Threatening Skin and Soft-Tissue Infections

Group A β-hemolytic streptococcal gangrene. Group A β-hemolytic streptococcal gangrene is an extremely rapid–progressing skin and soft-tissue infection (figure 1). The causative organisms secrete hemolysins, streptolysins O and S (which are cardiotoxic), and leukocidins. Gangrene results when the cutaneous blood vessels thrombose, and this finding is often associated with intense local pain. The involved skin is initially erythematous and indurated but, if treatment is delayed, quickly evolves to contain hemorrhagic blebs with focal necrotic zones (figures 2 and 3). The potential for extensive tissue loss and mortality exists, especially if treatment is delayed. Therefore, prompt, aggressive tissue debridement and antibiotic therapy are necessary for a favorable outcome (table 1).

Clostridial myonecrosis ("gas gangrene"). Clostridial myonecrosis is a destructive infectious process of muscle associated with infections of the skin and soft tissues. It is often associated with local crepitance and systemic signs of toxemia, which are caused by the anaerobic, gas-forming bacilli of the *Clostridium* genus. This infection most often occurs after abdominal operations on the gastrointestinal tract; however, penetrating trauma, such as gunshot wounds and frostbite, can expose muscle, fascia, and subcutaneous tissues to these organisms. Common to all of these conditions is an environment containing tissue necrosis, low oxygen tension, and sufficient nutrients (amino acids and calcium) to allow germination of clostridial spores and production of the lethal α-toxin.

Clostridia are gram-positive, spore-forming, obligate anaerobes that are widely found in soil contaminated with animal excretia. They may also be isolated from the human gastrointestinal tract and from the skin in the perineal area. *Clostridium perfringens* is the most common isolate (present in 80% of cases) and is among the fastest-growing clostridial species, with a gen-

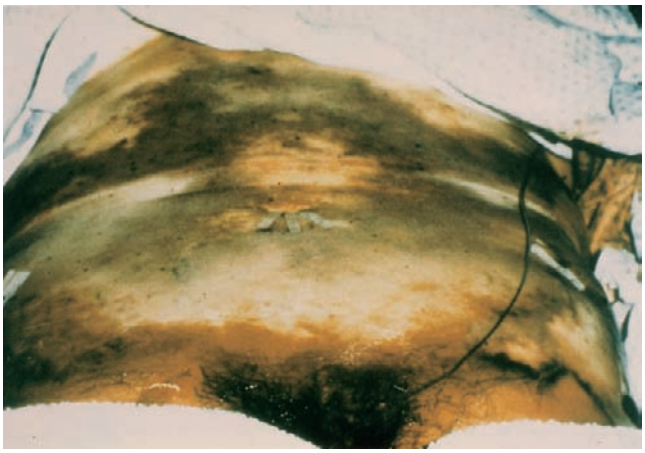

Figure 3. Streptococcal gangrene of the abdominal wall following an elective operative procedure. The incision can be seen in the umbilical area, with tape strips covering it.

Figure 4. Clostridial myonecrosis ("gas gangrene") following emergent surgery for penetrating abdominal trauma. At debridement, all layers of the abdominal wall were involved.

Table 1. Antibiotic treatment regimens for commonly encountered soft-tissue infections and surgical site infections.

Type of infection	Common infecting bacteria	Antibiotic therapy[a]
Superficial wound and surgical incision infections	Streptococci, staphylococci	Not used routinely; if needed, first-generation cephalosporin (e.g., cefazolin iv or oral cephalexin), penicillinase-resistant penicillin (e.g., methicillin iv or oral oxacillin)
Deep wound infections		
Other than after gastrointestinal, female genital tract, or oropharyngeal surgery	Streptococci, staphylococci,[b] gram-negative enteric bacteria possible	First-generation cephalosporin or methicillin iv; if mixed infections are suspected or seen on Gram stain, second- or third-generation cephalosporin (e.g., cefoxitin or ceftizoxime iv) or ampicillin-sulbactam, ticarcillin-clavulanate, or piperacillin-tazobactam iv[c]
After gastrointestinal, female genital tract, or oropharyngeal surgery	Same as for other deep wound infections, with the addition of *Bacteroides* species, other anaerobes, enterococci	Same as for mixed infection, above[c]
Gangrenous infections: onset of clinical findings is 24–48 h (acute) after trauma or operation	Group A β-hemolytic streptococci, clostridia	Penicillin G (high doses) iv
Necrotizing infections[d]: onset of clinical findings is $\geq$4 days (subacute) after trauma or operation	Polymicrobial; aerobic and anaerobic bacteria	Same as for mixed infection, above[c]

[a] Initial prompt surgical treatment, including drainage and debridement, is of primary importance in management of surgical wound infections and should be repeated as necessary during hospital stay.
[b] Vancomycin should be used if methicillin-resistant *Staphylococcus aureus* or *Staphylococcus epidermidis* is isolated, especially when the infection is associated with prosthetic implants. If vancomycin resistance is noted, agents such as quinupristin-dalfopristin can be used.
[c] In cases of nosocomial infections or primary antibiotic treatment failure, the use of imipenem-cilistatin or meropenem iv should be considered.
[d] Includes Fournier's gangrene.

eration time, under ideal conditions, of ~8 min. This organism produces collagenases and proteases that cause widespread tissue destruction, as well as α-toxin, which has a role in the high mortality rate associated with clostridial myonecrosis. The α-toxin causes extensive capillary destruction and hemolysis, leading to necrosis of the muscle and overlying fascia, skin, and subcutaneous tissues.

Historically, clostridial myonecrosis was a disease associated with battle injuries, but 60% of cases now occur after trauma—50% of these after automobile accidents and the remainder after crush injuries, industrial accidents, and gunshot wounds. Mortality can be the result of a failure to recognize that clostridial infection is occurring, which leads to a delay in the debridement of devitalized tissues. Patients often complain of a sudden onset of pain at the site of trauma or the surgical wound, which rapidly increases in severity and extends beyond the original borders of the wound. The skin initially becomes edematous and tense; its pale appearance progresses to a magenta hue. Hemorrhagic bullae are common, as is a thin, watery, foul-smelling discharge (figure 4). Examination of the wound discharge by Gram staining reveals abundant large, gram-positive rods with a paucity of surrounding leukocytes.

The definitive diagnosis of gas gangrene is based on the appearance of the muscle on direct visualization by surgical exposure, because many of the changes associated with such infections are not apparent when the tissue is inspected through a small traumatic wound. Initially, the muscle is pale, edematous, and unresponsive to stimulation. As the disease process continues, the muscle becomes frankly gangrenous, black, and extremely friable. This occurs, however, very late and is often accompanied by septicemia and shock. Despite profound hypotension, renal failure, and other evidence of organ failure, these patients may be remarkably alert and extremely sensitive to their surroundings. They may be aware of the increasing severity of their condition and often panic just before slipping into toxic delirium and, eventually, coma.

These clinical features should arouse suspicion early in the course of the disease, so that it can be recognized and aggressive surgical debridement can be undertaken. Gas in the wound is a relatively late finding, and by the time crepitance is appreciated, the patient may be near death. Approximately 15% of these patients have positive blood culture results, but this, too, is a late finding. Serum creatine kinase levels, although relatively nonspecific, are always elevated in cases with muscle involvement.

The mortality rate associated with gas gangrene approaches 60%. It is highest in cases involving the abdominal wall and lowest in cases affecting the extremities. Among the signs that predict a poor outcome are leukopenia, thrombocytopenia, hemolysis, and severe renal failure. Myoglobinuria is common and can contribute significantly to worsening of renal function. Frank hemorrhage may also be present and is a harbinger of disseminated intravascular coagulation.

Successful treatment of this life-threatening infection depends on early recognition and debridement of all devitalized

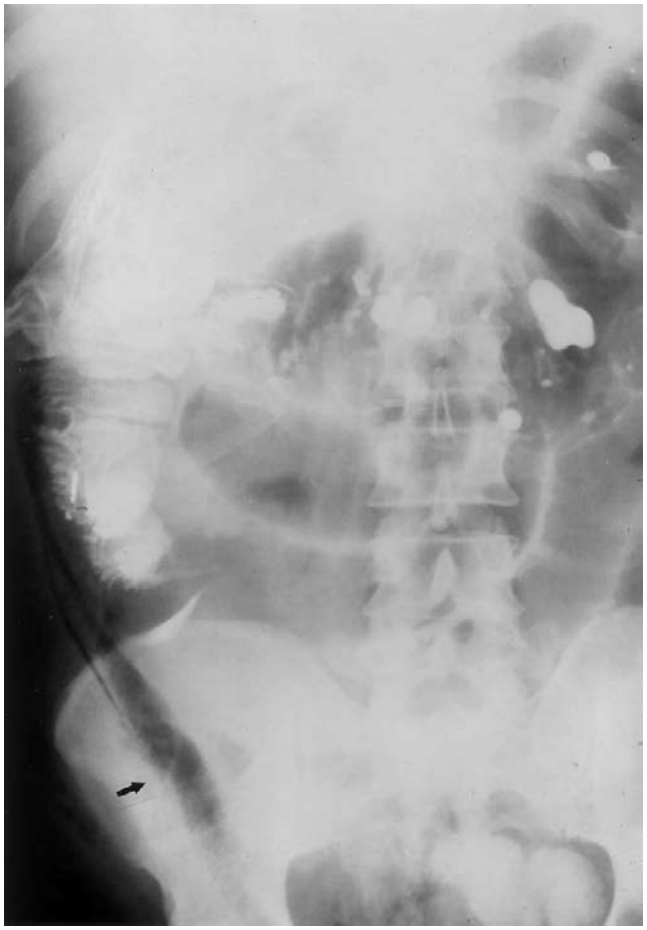

Figure 5. Abdominal radiograph showing air in the right side of the abdominal wall *(arrow)* in a patient with clostridial fasciitis following elective cholecystectomy.

and infected tissues. When extremities are involved, amputation is frequently indicated. Hyperbaric oxygen (100% oxygen at 3 atm) has been reported to reduce associated tissue loss and mortality; however, the mainstay of treatment is surgical debridement, and this should never be delayed while arrangements for hyperbaric oxygen treatments are made. A parenteral antibiotic directed at the causative organism should be administered (table 1). Cardiovascular collapse mandates iv fluid resuscitation with large volumes. Failure to adequately resuscitate these patients compromises therapy by limiting oxygen delivery and antibiotic distribution to the affected tissues and may promote progression to multisystem organ failure.

A less life-threatening form of this disease is known as clostridial cellulitis [4]. In this process, the bacterial tissue invasion is primarily superficial to the fascial layer, without muscle involvement. Prompt recognition and treatment, as described earlier, can reduce the associated morbidity and mortality. In rare patients, the clostridia involve initially only the fascia, sparing the skin and muscle layers (figures 5 and 6).

Necrotizing fasciitis. Necrotizing fasciitis is an aggressive soft-tissue infection involving the fascia, with characteristic extensive undermining and tracking along anatomic planes. This process usually occurs in patients with significant comorbidity, such as diabetes mellitus or peripheral vascular disease, but it is also seen in obese or malnourished patients and in iv drug abusers. Superficial cellulitis is initially seen, with progressive necrosis of the underlying subcutaneous tissue resulting from the thrombosis of the perforating vessels. Classically associated with group A β-hemolytic streptococci and staphylococci, the disease is now known to be caused by a variety of organisms, including aerobic streptococci, staphylococci, and coliforms, as well as anaerobic *Peptostreptococcus* and *Bacteroides* species. Ninety percent of these infections are polymicrobial, and it is common to obtain up to 15 organisms from cultures of samples from the fascial planes involved in these infections.

Necrotizing fasciitis most commonly evolves from a benign-appearing skin lesion (80% of cases). Minor abrasions, insect bites, injection sites, and perineal abscesses have all been implicated [5]. Rare cases have been reported in women with Bartholin's gland abscess, from which the infection has spread to fascial planes of the perineum and thigh. Surgical procedures, especially bowel resections and penetrating trauma, can be complicated by superficial wound infections that evolve into necrotizing fasciitis. The infection commonly involves the buttocks and perineum, resulting from untreated perirectal abscesses or decubitus ulcers. Intravenous drug abusers commonly participate in "skin popping," which leads to infections of the upper extremities. The remaining 20% of patients have no visible skin lesion.

The initial presentation is that of a slowly advancing cellulitis

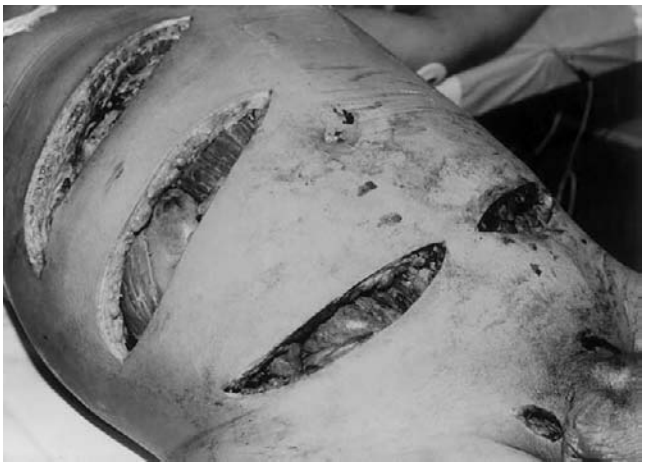

Figure 6. Patient whose radiograph was shown in figure 5. Multiple incisions were made to remove all necrotic fascia. Overlying skin, subcutaneous tissue, and deeper muscle layers were found not to be involved with the infection. Therefore, debridement only involved removing the fascial layer, which has already been excised here.

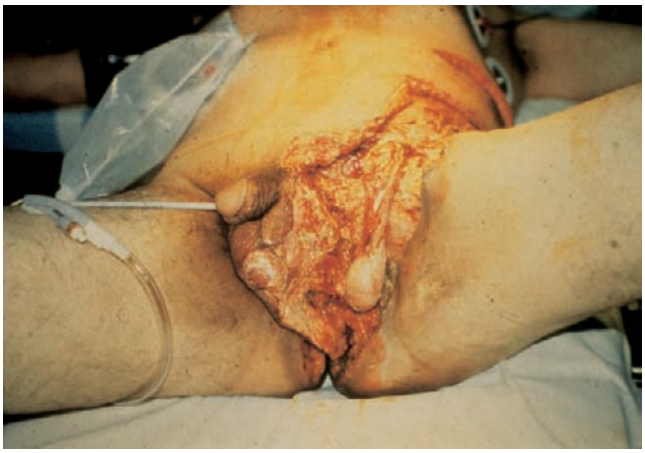

Figure 7. Diabetic patient who developed necrotizing fasciitis after drainage of perirectal abscess. Initial debridement has been done, in addition to a diverting colostomy.

that progresses to a firm, tense, "woody" induration of the subcutaneous tissues. This entity may be distinguished from other aggressive anaerobic soft-tissue infections (e.g., synergistic necrotizing cellulitis) by the presence of a brawny, pale, erythematous appearance of the skin overlying the subcutaneous tissues, which are unyielding, making fascial planes and muscle groups indistinguishable on palpation. Often, a broad erythematous tract along the route of the underlying fascial plane can be discerned through the skin. If an open wound exists, probing the edges with a blunt instrument permits ready dissection of the superficial fascia well beyond the wound margins, and this is the most important diagnostic feature of necrotizing fasciitis. On direct inspection, the fascia is swollen and dull gray, with stringy areas of fat necrosis. A thin, brown exudate can be expressed from the wound, whereas frank purulent drainage is rare.

As with other life-threatening soft-tissue infections, the most important component of the treatment plan is aggressive, total debridement of all devitalized and necrotic tissue (figures 7 and 8). This infection necessitates frequent operations and dressing changes. Wide debridement and parenteral antibiotics have a profound effect on survival, and limited or staged debridement has no place in the treatment of this very aggressive, life-threatening infection. Parenteral antibiotics (table 1) should be directed against the polymicrobial aerobic and anaerobic microorganisms isolated from these infections. Every effort should be made to quickly identify the offending organisms, and antibiotic therapy should be adjusted accordingly.

Special emphasis should be placed on the rarely reported monomicrobial form of this disease, known as "idiopathic" or "spontaneous" necrotizing fasciitis. When erythema, induration, and warmth occur in the absence of trauma or another obvious cause for the infection, this entity must be considered, because it often arises without any obvious portal of entry. Misdiagnosis and delay in diagnosis are common (this disease is often mistaken for arthritis) and are associated with significant morbidity and mortality (figure 9). Surgical exploration with debridement of infected and necrotic tissue, in addition to systemic antibiotic therapy directed toward the aerobic *Streptococcus* organism, can result in decreased morbidity and mortality (table 1).

Special Circumstances

Fournier's gangrene. Necrotizing fasciitis that originates as a necrotic black area on the scrotum of male patients most often has a cryptogenic origin. In our experience, Fournier's gangrene occurs more commonly without a predisposing event or after routine uncomplicated hemorrhoidectomy. Less commonly, this condition has occurred after urologic manipulation or as a late complication of deep anorectal suppuration. Fournier's gangrene is characterized by necrosis of the skin and soft-tissues of the scrotum and/or perineum that is associated with a fulminant, painful, and severely toxic infection. Definitive diagnosis is made by identification of a necrotic black area on

Figure 8. Patient shown in figure 7. Daily inspection and additional debridements were done as indicated.

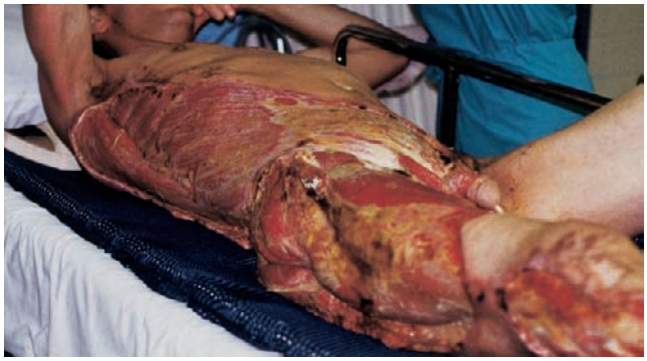

Figure 9. Extensive tissue loss in a patient who developed spontaneous group A streptococcal idiopathic necrotizing fasciitis.

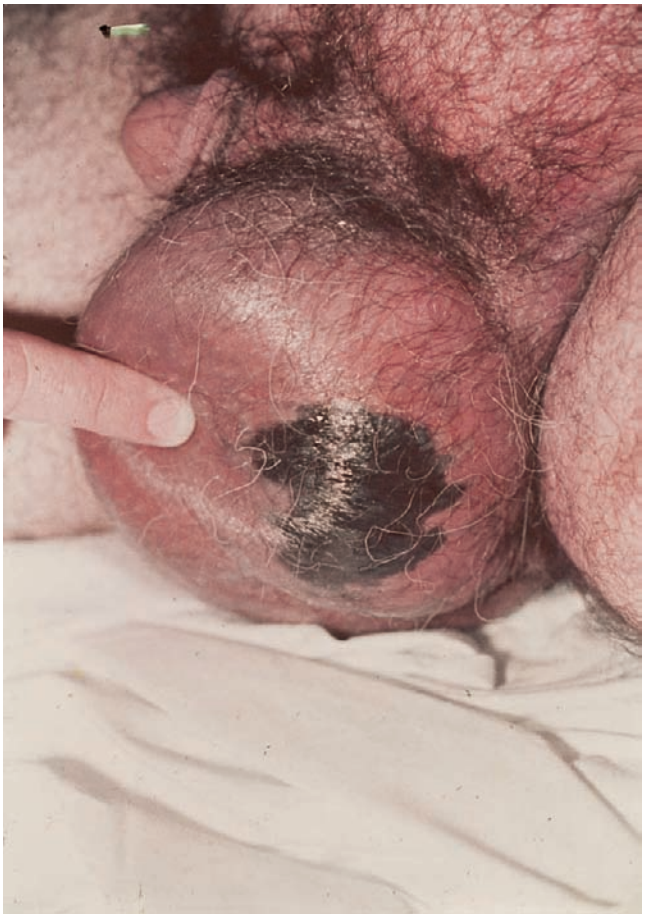

Figure 10. Fournier's gangrene, with pathognomonic "black spot" on the involved scrotum. Tissue loss at debridement in this patient was limited to the scrotum.

the scrotum that is associated with local and systemic signs of infection (figures 10–12). If the infection is left untreated, death ensues from uncontrolled, severe systemic sepsis and multiple organ failure. Prompt recognition and treatment can minimize tissue loss, specifically of the skin and soft tissues of the scrotum and perineum, and may prevent complete loss of genitalia.

The infection is often polymicrobial, as with necrotizing fasciitis, with several species of aerobic and anaerobic bacteria predominating. Successful treatment is, again, based on early recognition and vigorous surgical debridement, often including diversion of the fecal stream. Empirical antibiotic treatment is appropriate until results of culture and susceptibility testing are available (table 1). The therapeutic benefit of hyperbaric oxygen treatments remains to be proven for this clinical entity.

Ecthyma gangrenosum. Occasionally, hospitalized patients with overwhelming pseudomonal septicemia develop a patchy dermal and subcutaneous necrosis. Although sepsis caused by *Pseudomonas aeruginosa* is often indistinguishable from other types of gram-negative sepsis, a characteristic skin lesion may develop, with erythematous macular eruptions that quickly become bullous with central ulceration and necrosis [6]. This lesion may resemble a decubitus ulcer with the characteristic black eschar (figure 13). There are usually multiple lesions occurring in different stages of development, which may concentrate on the extremities or the head and neck (figure 14). These lesions may be distinguished from the lesions of pyoderma gangrenosum (a noninfectious dermatosis) by their association with clinical signs of infection (i.e., fever and leukocytosis) in addition to the isolation of *P. aeruginosa* from culture of the lesion. Treatment is primarily by administration of antimicrobial therapy (table 1) and by debridement of multiple lesions (in selected patients), which may lessen the bacterial burden, perhaps allowing greater antibiotic efficacy.

SSIs

The incidence of wound infection varies from surgeon to surgeon, from hospital to hospital, from one surgical procedure to another, and most important, from one patient to another. Patient risk factors and preventative techniques for the development of SSIs have been discussed elsewhere [7]. The Centers for Disease Control and Prevention definition of surgical wound infection was modified to SSI in 1992 [8]. SSIs are classified into 2 groups: (1) incisional and (2) organ and organ/space. The incisional SSIs are further divided into superficial (skin and subcutaneous tissue) and deep (deep soft tissue–muscle and fascia). Often the diagnosis of deep infection can be made only at the time of surgical explorations. Lack of response to antibiotics alone may be a sign of a deep infection that requires surgical drainage and debridement. Detailed criteria for defining these types of SSI are offered elsewhere [9]. These definitions should be universally followed so that the proper surveillance, prevention, and control of SSIs can be carried out. The pathogens that are isolated from SSIs vary with

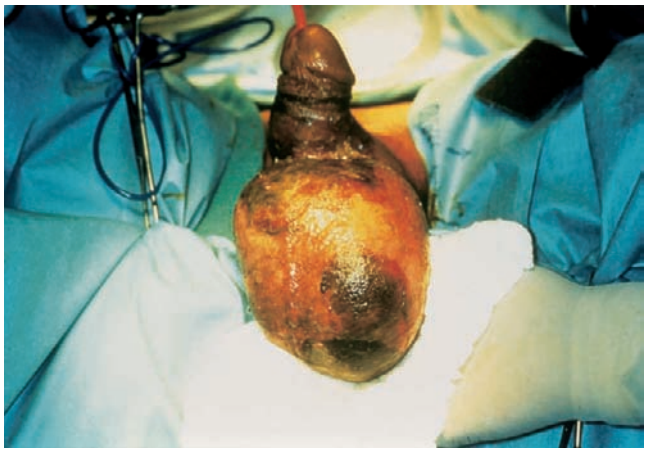

Figure 11. Far-advanced Fournier's gangrene of the scrotum (not the same patient shown in figure 10).

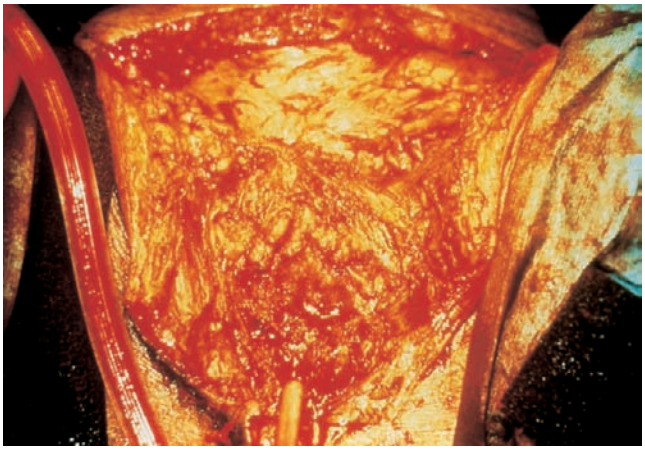

Figure 12. Tissue loss in the patient shown in figure 11 resulted in the need to debride all of the genital organs. A Foley catheter, which had been placed into the bladder, is seen at bottom.

the type of surgical procedure. *S. aureus* from the exogenous environment or the patient's skin flora is the usual cause of infections associated with clean surgical procedures in which the gastrointestinal, gynecologic, and respiratory tracts have not been entered. A polymicrobial aerobic-anaerobic flora that closely resembles the normal endogenous microflora of the surgically resected organ is most frequently found in association with the other categories of surgical procedures, including clean-contaminated, contaminated, and dirty-infected. Clinically, these SSIs are heralded by the classic or cardinal signs of inflammation: rubor, calor, dolor, tumor, and loss of function *(functio laesa)*.

According to the data from the National Nosocomial Infections Surveillance system, there has been little change in the incidence and distribution of the pathogens isolated from SSIs during the 1990s [9]. More of these pathogens do, however, show antimicrobial resistance, and the presence of methicillin-resistant *S. aureus* (MRSA) in particular has increased [10]. The chronology of resistance of gram-positive bacteria is shown in table 2. Vancomycin-resistant microorganisms isolated from infections in surgical patients require careful attention to time-honored techniques, such as hand washing, as well as the use of effective antimicrobials [11–13]. Organisms commonly isolated from skin and soft-tissue infections that occur after operations and proposed treatment regimens are listed in table 1.

THERAPEUTIC OPTIONS FOR RESISTANT GRAM-POSITIVE INFECTIONS

MRSA has been reported to account for up to 21% of nosocomial skin infections [14]. The increased prevalence of MRSA has narrowed the treatment options for patients with serious infections, in particular because these infections are frequently cross-resistant to the majority of antibiotic agents. As a result, the glycopeptides vancomycin and teicoplanin (not available in the United States) are now used to treat skin and soft-tissue infections caused by MRSA or multidrug-resistant pathogens. Vancomycin typically is the drug of choice for methicillin-resistant coagulase-negative and coagulase-positive staphylococcal infections [15]. It is also useful against penicillin-resistant streptococcal infections.

However, vancomycin resistance has increased progressively over the past 2 decades with the development of vancomycin-resistant *Enterococcus faecium* (VREF). Approximately one-half of all *E. faecium* infections in the United States are resistant to vancomycin [16]. There is no standard treatment for infections caused by VREF, because these pathogens are typically multidrug-resistant. In addition, strains of *S. aureus* with reduced susceptibility to vancomycin (*S. aureus* intermediately resistant to glycopeptides) were identified in France, Japan, and the

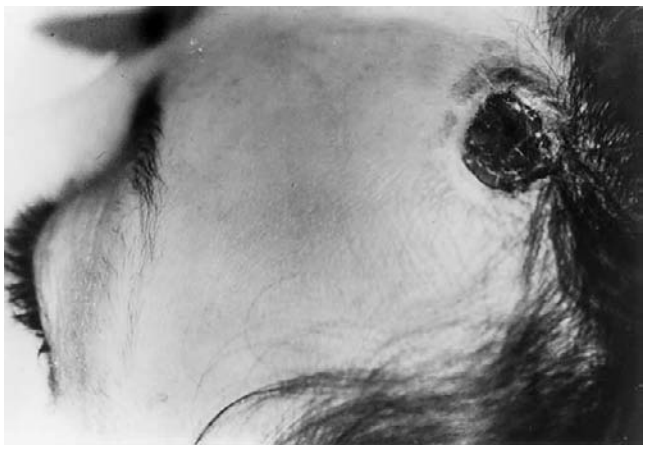

Figure 13. Circular eschar-like lesion on the forehead of a patient with ecthyma gangrenosum and disseminated *Pseudomonas* infection.

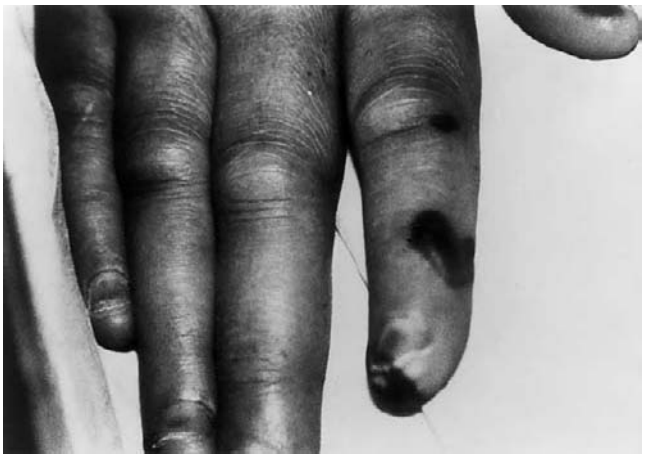

Figure 14. The hand of the patient shown in figure 13, with various stages of cutaneous ecthyma gangrenosum.

Table 2. Chronology of gram-positive bacterial resistance.

Year/decade	Event
1950s	Resistance to penicillin is observed
1960s	Resistance to methicillin is recognized
1980s	Methicillin resistance becomes endemic at large teaching centers
1990s	Vancomycin-resistant enterococci emerges as nosocomial pathogen
1994	CDC (HICPAC) recommendations to control vancomycin-resistant enterococci are published
1995	Vancomycin-resistant *Staphylococcus aureus* is produced in laboratory
1996–1997	Clinical isolates of vancomycin-resistant *S. aureus* are seen

NOTE. CDC, Centers for Disease Control and Prevention; HICPAC, Healthcare (previously Hospital) Infection Control Practices Advisory Committee.

United States in the mid-1990s [17–20]. MRSA isolates with decreased teicoplanin susceptibility have also been reported [21]. This resistance to glycopeptides may have arisen as a result of overuse and inappropriate use of vancomycin.

Even when the infecting organism is susceptible, glycopeptides are not ideal antibiotic agents for every patient. Side effects of vancomycin use, for example, nephrotoxicity and ototoxicity (especially when vancomycin is used in combination with other nephrotoxic and ototoxic drugs, such as aminoglycosides) and "red man syndrome," are more commonly reported in association with use of preparations available before 1990 [22, 23].

Quinupristin-dalfopristin (Synercid) is the first injectable streptogramin available for the treatment of complicated gram-positive skin and skin structure infections. The antimicrobial spectrum of quinupristin-dalfopristin makes it a particularly useful option in the treatment of infections caused by VREF and *S. aureus* that is intermediately resistant to glycopeptides. Two randomized, multicenter studies compared the efficacy of quinupristin-dalfopristin with that of standard therapies in the treatment of 893 patients who had complicated skin and skin structure infections [12]. The clinical success rate was 68.2% with quinupristin-dalfopristin and 70.7% with standard regimens that included vancomycin (95% CI, −10.1, 5.1). Clinical success, with eradication or presumed eradication of the pathogens, was achieved in statistically equivalent percentages of patients treated with quinupristin-dalfopristin (63.2%) and standard therapies (67.1%). Bacteriologic outcomes were comparable for quinupristin-dalfopristin (66.7%) and vancomycin (64.7%). The most common quinupristin-dalfopristin-related adverse events were nausea (6.2%), vomiting (3.8%), rash (3.1%), pain (3.1%), and pruritus (2.7%). A total of 66.2% (298 of 450) of patients who received iv quinupristin-dalfopristin experienced local venous intolerability, which was noted at a higher incidence when peripheral veins were used for administration. Although quinupristin-dalfopristin can be associated with venous irritation when it is administered via a peripheral iv catheter, there are management options that help to limit this adverse event. These include administration of the drug in a larger volume of liquid, administration by use of a central catheter or a peripherally inserted venous catheter, and a change in infusion site [24].

Quinupristin-dalfopristin has proved to be particularly efficacious in the treatment of VREF. In a noncomparative phase III and emergency-use study involving seriously ill patients with VREF, the infections of 73.6% of patients responded to quinupristin-dalfopristin therapy. The overall by-pathogen bacteriologic response rate was 70.4% [25]. The most common treatment-related adverse events were arthralgia (9.1%) and myalgia (6.6%). Potential drawbacks of quinupristin-dalfopristin use appear to be that it is bacteriostatic rather than bactericidal against vancomycin-resistant enterococci, it is not effective against *E. faecalis,* and only iv preparations are available.

Preliminary publications indicate that the oxazolidinone linezolid also shows promise in the treatment of skin and skin structure infections [26]. In patients with skin infections predominantly caused by *S. aureus,* including MRSA, microbiological and clinical success was achieved in >80% of patients treated with linezolid. Linezolid was also effective against VREF in unpublished comparative and compassionate-use studies that included patients with skin and skin structure infections [26]. One potential drawback associated with linezolid is that it is bacteriostatic rather than bactericidal against *E. faecium* and *S. aureus.*

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