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Complicated skin and soft-tissue infections: Diagnostic approach and empiric treatment options

ABSTRACT

Skin and soft-tissue infections are common and generally are uncomplicated at the time of initial presentation. However, these infections can worsen quickly when there are delays in presentation and treatment. Upon encountering these infections, physicians must respond quickly with an appropriate therapeutic plan and be aware of trends in microbial resistance in order to optimize patient care.

KEY POINTS

The primary challenge in managing skin and soft-tissue infections is to avoid delays in diagnosis and thereby prevent uncomplicated infections from progressing.

The necessary course of action can include hospitalization, prompt initiation of antimicrobial therapy, and surgical consultation.

Many patients with skin and soft-tissue infections will require surgical intervention for successful treatment.

The recent proliferation of community-acquired methicillin-resistant *Staphylococcus aureus* strains has influenced the choice of antimicrobial therapy.

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Primary care physicians are often the first to encounter patients with skin and soft-tissue infections. Many uncomplicated superficial infections resolve spontaneously with local care. Determining an exact etiology for these simple infections is often difficult and usually not necessary. Patients with these infections typically present to the physician's office or emergency department after noticing a painful red area involving the skin that has not resolved or is worsening. The initial goal should be to assess whether the patient is more seriously ill and thus harboring a more complicated infection that requires emergent intervention. If signs and symptoms of systemic involvement are present—specifically, fever, tachycardia, or hypotension—immediate hospitalization and treatment with intravenous antibiotics is necessary.

This article discusses the importance of distinguishing between complicated and less serious infections of the skin and soft tissue and reviews the microbiology, diagnosis, and empiric treatment of these infections.

DISTINGUISHING COMPLICATED INFECTIONS

Complicated skin and soft-tissue infections have been defined by the US Food and Drug Administration (FDA) using its Center for Drug Evaluation and Research criteria.[1] Specifically, there are five generally accepted conditions that identify complicated infections:

- Involvement of deep tissues, including subcutaneous fat
- Need for significant surgical intervention
- Involvement of the perianal area
- Infection of the foot in a diabetic patient
- Presence of significant coexisting diseases, including diabetes mellitus, an immunocompromised state, and obesity.

These criteria generally include patients with surgical site infection, necrotizing soft-tissue infection, and signs of systemic toxicity.

Identifying the cause of infection or the type of injury that has led to a complicated skin or soft-tissue

infection can help in discerning the likely causative organisms and guiding treatment decisions. Although these infections can be quite varied, they share a common host response that includes signs of local inflammation (erythema, edema, warmth, and tenderness) and, for more advanced infections, signs of systemic toxicity (fatigue, malaise, fever, tachycardia, and hypotension).

Uncomplicated skin infections

Uncomplicated skin infections include impetigo, erysipelas, folliculitis, furunculosis, and, in some cases, superficial cellulitis.[2–5]

Impetigo is an infection of the epidermis that can cause blisters or bullae. Erysipelas involves the dermal layer of the skin and generally presents as a painful erythematous, slightly raised lesion. Folliculitis is a superficial infection of the hair follicle, whereas furuncles are deeper infections of a single hair follicle that frequently will drain spontaneously with local care.

More complicated skin infections

More complicated skin infections include cellulitis, lymphangitis, and carbuncles.[6]

Cellulitis is a catch-all description that can include uncomplicated infections involving only the epidermis and dermis, as well as more complicated infections extending to the subcutaneous tissues. Patients with deeper infections, such as necrotizing fasciitis, septic arthritis, and osteomyelitis, often will have overlying cellulitis. Cellulitis also can occur as a response to a variety of deep inflammatory diseases that are not infectious. Therefore, patients who present with cellulitis require immediate and thorough attention in order to determine the cause, which is crucial to determining whether hospitalization, intravenous antimicrobial therapy, or surgical intervention is required.

Lymphangitis is an infection of the subcutaneous lymphatic channels and presents with erythematous streaks that are usually tender and accompanied by lymphadenopathy.

Carbuncles, like furuncles, can occur anywhere on the hairy skin. They usually extend to involve several adjacent hair follicles, which results in a coalescent inflammatory mass with multiple areas of drainage. Carbuncles tend to develop on the back of the neck and are especially likely to occur in patients with diabetes mellitus. They are generally treated with antimicrobials and incision and drainage.

Soft-tissue infections

Perianal abscesses. Isolated perianal abscesses generally are caused by cryptoglandular disease and often can be treated by simple incision and drainage.[7] Antibiotics are not necessary unless the patient has extensive surrounding cellulitis or significant coexisting diseases such as diabetes, HIV infection, or an otherwise immunocompromised state. More extensive perianal abscesses that involve deeper tissues, that have extensive surrounding cellulitis, or that occur in diabetics or otherwise immunocompromised patients require immediate surgical consultation, surgical drainage, and antimicrobial therapy.

Diabetic foot infections generally result from trauma to an insensate foot or from secondary infection of foot ulcers.[8,9] These infections can be superficial, but many involve the deeper tissues. The astute diabetic patient is generally mindful of changes consistent with superficial infection. Deeper infections may go unnoticed, however, because of a lack of sensation in the involved extremity. Any diabetic patient presenting with a lower extremity infection needs careful evaluation to rule out involvement of the deeper tissues. The deep spaces of the feet can be involved but show only subtle external signs of infection.

Underlying osteomyelitis is common in patients with diabetic foot infections and must be ruled out with careful clinical examination and radiologic studies.[8,9] A positive "probe to bone" test is a simple and highly specific correlate of osteomyelitis underlying a diabetic foot ulcer.[10] It involves lightly palpating for the presence or absence of underlying bone using a sterile instrument. When the probe detects a "rock-hard" or "gritty" structure, the presence of bone—and, by definition, osteomyelitis—is confirmed.[10]

Necrotizing soft-tissue infections are uncommon but serious and life-threatening.[11,12] Early diagnosis and rapid surgical intervention has been shown to reduce mortality. Any suspicion of a necrotizing infection should prompt immediate initiation of broad-spectrum antibiotic therapy and surgical consultation.

Early manifestations of necrotizing soft-tissue infections include tachycardia, low-grade fever, pain that is disproportionate to physical findings, and leukocytosis. The classic presentation of skin blisters, ecchymosis, bullae, or crepitus (a crackling sensation under the skin) is very specific for a necrotizing process but is present in only 10% to 40% of patients.[12] Rapid progression of these skin changes is an important and ominous sign. The presence of gas in soft tissue on computed tomography (CT) or of fascial necrosis on magnetic resonance imaging (MRI) can be diagnostic of a necrotizing soft-tissue infection in patients presenting with more subtle physical findings.

Broad-spectrum antimicrobial therapy and prompt

surgical debridement are the mainstays of treatment for patients with necrotizing soft-tissue infections. Patients showing signs of physiologic decline should be resuscitated and managed in an intensive care environment. Amputation may be necessary in up to one third of patients with necrotizing soft-tissue infections involving the extremities. Careful wound observation and repeated surgical debridement is necessary and has been shown to reduce mortality.[13]

MICROBIOLOGY

The most common skin and soft-tissue infections encountered by primary care physicians are listed in **Table 1** along with their associated causative organisms.

Skin infections. Erysipelas generally is caused by streptococcal species, usually *Streptococcus pyogenes*. Cellulitis can be caused by numerous indigenous skin organisms, which vary depending on location. Cellulitis associated with furuncles, carbuncles, or abscesses is usually caused by *Staphylococcus aureus*. More diffuse cellulitis can be caused by either streptococci or *S aureus*. Any drainage should be cultured to identify the causative organism. Although aspiration of skin has been recommended in patients with cellulitis, it is unlikely to reveal an organism and is rarely performed in practice. Blood cultures also are frequently recommended but are positive in less than 5% of cases.[6,14]

Perianal infections often are polymicrobial and usually are caused by a mix of gram-positive and gram-negative organisms, including both aerobic and anaerobic species. These infections require broader-spectrum therapy compared with cellulitis.[2,15]

Diabetic foot infections generally have involvement by *S aureus*, but studies in patients with these infections frequently identify a variety of other organisms, particularly gram-negative species. Interestingly, despite these findings, randomized controlled trials have demonstrated that treatment aimed at gram-positive species is associated with the same clinical response as broader-spectrum therapy. This suggests that many, if not all, of the gram-negative organisms identified are colonizers rather than pathogens.

Surgical site infections are caused by a variety of organisms; the type and site of operation often dictate which organisms are suspected. Infections in patients who have had clean operations frequently are caused by gram-positive organisms; in contrast, infections from operations on the gastrointestinal or genitourinary tract may be caused by gram-positive and gram-negative organisms as either monomicrobial or mixed infections.[16] The organisms most frequently implicated in surgical site infections are gram-positive and include *S aureus*, coagulase-negative staphylococci, and enterococci. Other organisms involved include *Escherichia coli* and a variety of gram-negative enteric bacteria.

TABLE 1
Microbiology of common skin and soft-tissue infections

Type of infection	Common organisms
Folliculitis	*Staphylococcus aureus*
Furuncles and carbuncles	*S aureus*
Impetigo and erysipelas	Beta-hemolytic streptococci, *S aureus*
Lymphangitis	Group A streptococci, *S aureus*
Cellulitis	Beta-hemolytic streptococci, *S aureus, Haemophilus influenzae, Staphylococcus epidermidis*
Human bites	*S aureus, S epidermidis,* streptococci (alpha- and beta-hemolytic), *Corynebacterium* spp, *Eikenella corrodens, Bacteroides fragilis*
Domestic pet bites	*Pasteurella multocida*
Abscess from intravenous drug use	*S aureus*
Diabetic foot infections	*S aureus, S epidermidis,* gram-negative bacilli

Although they are uncommon causes of surgical site infection, *S pyogenes* and *Clostridium perfringens* can lead to infection within 48 hours of operation.[17,18] Patients with infections due to these organisms usually will have minimal signs of infection at the surgical site but will report disproportionate pain and tenderness at the surgical site and show signs of systemic toxicity. Treatment involves opening the incision and performing cultures. High-dose penicillin therapy should be instituted immediately. The drainage is usually watery and has been described as "dishwater pus." If not attended to promptly, these infections progress rapidly and frequently result in death. The associated skin findings of necrotizing soft-tissue infections, such as bullae and necrosis, develop extremely late in these infections.

Necrotizing soft-tissue infections involve a variety of aerobic, facultative, and anaerobic organisms. Initial treatment with broad-spectrum antibiotics and cultures of the involved tissue are necessary because of the difficulty of predicting which organisms may be involved in a specific infection. *S pyogenes* is isolated as the single causative organism in more than half of

TABLE 2
Conditions that predispose to weakened host defenses

Diabetes mellitus	Organ transplantation
Chronic renal failure	HIV infection
Chronic steroid use	Advanced age
Chronic immunosuppressive therapy	Malnourishment

these cases.[11] It has been estimated that 15% of patients with necrotizing soft-tissue infections will not have an identified source of infection.[11]

DIAGNOSIS

Signs, symptoms, and history-taking

The classic signs and symptoms of inflammation (erythema, edema, pain, tenderness, warmth) confirm the presence of an infection. Spreading erythema is particularly concerning. The history should elicit the following: any recent injury to the infected area, intravenous drug use, any history of bites, travel history, and exposure to freshwater or saltwater. In addition, the medical history must specifically ascertain the presence of conditions or factors that might predispose to weakened immunity, such as certain diseases and the use of certain medications, particularly steroids and other immunosuppressive drugs **(Table 2)**.

Physical exam: Look beyond the infection site

A thorough physical examination is essential. While it is tempting to focus on the area of infection, a careful broader examination may reveal the underlying cause of infection. The presence of cellulitis in the lower abdominal quadrants, the groin, or even the hips may be a sign of a more remote infection, such as an incarcerated hernia or colonic diverticulitis. The examination should describe the area involved, the presence of fluctuance or crepitus, associated findings in the skin (eg, purpura, necrosis), and whether or not there is tenderness. The presence of pain and tenderness disproportionate to the associated physical findings often signals an underlying necrotizing soft-tissue infection that requires immediate attention. Crepitus is highly suggestive of a necrotizing infection. Fluctuance (a wavelike motion of a cavity containing fluid) suggests localized purulent collection that requires drainage. The borders of the infection should be outlined with an ink pen, as such a marking can be used to monitor the spread of cellulitis or the response to treatment.

Laboratory studies

Patients with complicated infection should undergo laboratory studies.[2,9] These include a complete blood cell count with differential as well as creatinine, bicarbonate, creatine phosphokinase, and C-reactive protein levels. The white blood cell count and C-reactive protein level can be determined sequentially to follow the response to therapy. Additional laboratory studies should be performed as indicated.

Patients with systemic signs of infection should have two sets of blood cultures obtained, although these are positive only infrequently. Any purulent drainage should be sent for immediate Gram stain and definitive culture and sensitivity testing. Serum glucose should be determined and normalized in diabetics and other patients in whom hyperglycemia is suspected.

Laboratory studies have a poor predictive value for the diagnosis of necrotizing soft-tissue infections. Wong et al recently proposed an index composed of laboratory values to help discriminate between necrotizing and nonnecrotizing soft-tissue infections in patients with more subtle physical findings.[19] Using six serum parameters (white blood cell count and levels of C-reactive protein, hemoglobin, serum sodium, creatinine, and glucose), they developed a weighted score to determine the risk of having necrotizing fasciitis. Their score demonstrated a positive predictive value of 92%.[19] Others have demonstrated the importance of hyponatremia in identifying patients with complicated soft-tissue infections who may be at risk for a necrotizing infection.[20]

Diagnostic imaging: Selective use can be helpful

Diagnostic imaging can be revealing but should be used selectively. Plain radiographs are indicated in patients with diabetic foot infections to ascertain the presence of osteomyelitis.[21] Plain radiographs also are useful to determine the presence of air in the soft tissues, which suggests the need for urgent surgical debridement. While CT is helpful to identify gas and fluid collections, MRI is more specific for identifying the subtle changes associated with necrotizing soft-tissue infections.[22] MRI also is superior to CT in detecting involvement of the muscular fascia. These studies are unnecessary in patients with more superficial infections and in those for whom an operation has already been deemed necessary.

ANTIMICROBIAL TREATMENT

A general algorithm for the management of soft-tissue infections is presented in **Figure 1**. A variety of antimicrobial agents may be appropriate to treat skin

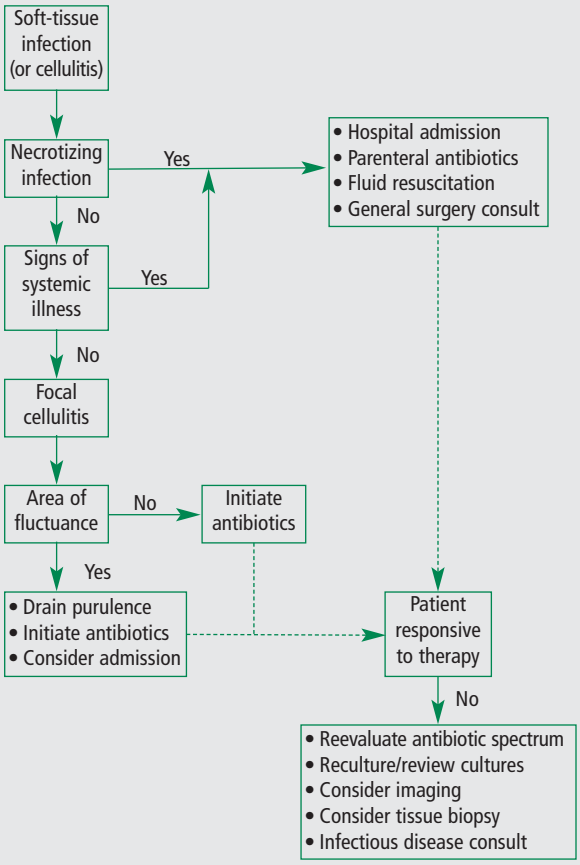

FIGURE 1. Algorithm for the management of soft-tissue infections.

and soft-tissue infections. The choice depends on the type of infection and the suspected pathogens. **Table 3** presents recommendations endorsed by the Infectious Diseases Society of America as of 2005.[2]

Penicillin is the treatment of choice for erysipelas. For cellulitis, a semisynthetic penicillin or first-generation cephalosporin should be used unless methicillin-resistant *S aureus* (MRSA) is suspected. The majority of cellulitis infections are caused by *S aureus*, but the incidence of methicillin resistance is increasing, even in community-acquired infections. In some areas of the United States, methicillin-resistant strains outnumber methicillin-sensitive strains by a 2:1 ratio.[2]

Differing approaches for community-acquired and hospital-acquired MRSA

Community-acquired MRSA can be treated with vancomycin, clindamycin, or trimethoprim-sulfamethoxazole.[23–25] Additional agents effective against community-acquired MRSA include tetracycline, linezolid (Zyvox), and gentamicin **(Table 4)**. Unfortunately, the use of gentamicin as a single agent can be associated with development of antimicrobial resistance, so gentamicin should be used only in combination.[23–25] Tigecycline (Tygacil), a new semisynthetic glycylcycline, may also represent a therapeutic option for patients hospitalized with complicated skin and skin-structure infections caused by community-acquired MRSA.[26,27]

In contrast, patients with hospital-acquired MRSA have a different antimicrobial sensitivity profile. These organisms remain sensitive to vancomycin, trimethoprim-sulfamethoxazole, tetracycline, and linezolid. Tigecycline also has been shown

TABLE 3
Recommended antimicrobial therapy for skin and soft-tissue *Staphylococcus aureus* infections in adults

Infections due to methicillin-sensitive *S aureus*	
Intravenous antibiotics	
Nafcillin (various) or oxacillin (various)	1–2 g every 4 hr
Cefazolin (various)	1 g every 8 hr
Clindamycin (various)	600 mg every 8 hr
Oral antibiotics	
Dicloxacillin (various)	500 mg 4 times daily
Cephalexin (various)	500 mg 4 times daily
Doxycycline (various) or minocycline (various)	100 mg twice daily
Trimethoprim-sulfamethoxazole (various)	1 or 2 double-strength tablets twice daily
Clindamycin	300–450 mg 3 times daily
Infections due to methicillin-resistant *S aureus*	
Intravenous antibiotics	
Vancomycin (various)	30 mg/kg/d in 2 divided doses
Linezolid (Zyvox)	600 mg every 12 hr
Clindamycin	600 mg every 8 hr
Daptomycin (Cubicin)	4 mg/kg every 24 hr
Oral antibiotics	
Linezolid	600 mg twice per day
Clindamycin	300–450 mg 3 times daily
Doxycycline or minocycline	100 mg twice daily
Trimethoprim-sulfamethoxazole	1 or 2 double-strength tablets twice daily

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TABLE 4
Pros and cons of drugs active against MRSA

Drug	Pros	Cons
Trimethoprim-sulfamethoxazole (various)	High efficacy, oral form, inexpensive	
Tetracycline (various)	High efficacy, oral form, inexpensive	Contraindicated in pregancy
Clindamycin (various)	Oral form, inexpensive	Effective vs community-acquired strains only, *Clostridium difficile*–associated colitis
Vancomycin (various)	High efficacy	IV only, ototoxicity, nephrotoxicity, expensive
Linezolid (Zyvox)	High efficacy, oral form	Myelosuppression (reversible), expensive
Daptomycin (Cubicin)	High efficacy, bactericidal	IV only
Gentamicin (various)		Moderate efficacy vs hospital-acquired strains, IV only, nephrotoxicity, ototoxicity
Tigecycline (Tygacil)	Active vs both gram-positive and gram-negative bacteria	IV only, expensive, contraindicated in pregnant women and children

MRSA = methicillin-resistant *Staphylococcus aureus*; IV = intravenous

to be effective against complicated skin and skin-structure infections caused by MRSA,[28] and the safety and efficacy of tigecycline monotherapy in these infections was recently established in two phase 3 studies.[29] Gentamicin resistance is more common, and most strains are not sensitive to clindamycin.[23–25] Most of the skin and soft-tissue infections that involve hospital-acquired MRSA do not involve other organisms.

Linezolid has been shown effective against skin and soft-tissue infections caused by MRSA. This should not be the first line of therapy, however, and should be considered only when there is culture-documented evidence of resistance or when there is nonresponse in a patient considered to be at high risk, such as with compromised immune function or prolonged exposure to an institutional environment. Daptomycin (Cubicin) has similar documented efficacy, and is bactericidal.[30,31]

TABLE 5
Recommended antimicrobial therapy for necrotizing infections in adults*

Mixed infection	
Ampicillin-sulbactam (various)	1.5–3.0 g every 6–8 hr
or	
piperacillin-tazobactam (Zosyn)	3.375 g every 6–8 hr
plus	
clindamycin (various)	600–900 mg every 8 hr
plus	
ciprofloxacin (various)	400 mg every 12 hr
Imipenem/cilastatin (Primaxin)	1 g every 6–8 hr
Meropenem (Merrem)	1 g every 8 hr
Ertapenem (Invanz)	1 g every day
Cefotaxime (various)	2 g every 6 hr
plus	
metronidazole (various)	500 mg every 6 hr
or	
clindamycin	600–900 mg every 8 hr
Streptococcal infection	
Penicillin (various)	2–4 million U every 4–6 hr
plus	
clindamycin	600–900 mg every 8 hr
***Staphylococcus aureus* infection**	
Nafcillin (various)	1–2 g every 4 hr
Oxacillin (various)	1–2 g every 4 hr
Cefazolin (various)	1 g every 8 hr
Vancomycin (various) (for resistant strains)	30 mg/kg/d in 2 divided doses
Clindamycin	600–900 mg every 8 hr
Clostridial infection	
Clindamycin	600–900 mg every 8 hr
Penicillin	2–4 million U every 4–6 hr

*All listed agents are given intravenously for these infections.

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Recommendations for specific soft-tissue infections

Perianal infections should be treated with broad-spectrum therapy if there is significant associated cellulitis. Few randomized clinical trials have assessed the treatment of these infections. The duration of therapy varies depending on the severity of infection. Patients with localized infections can be treated with incision and drainage alone. Patients with deep infections, diabetes, risk factors for compromised immune

function, or inflammatory bowel disease should be treated with a short course of therapy.

Diabetic foot infections respond well to agents that are effective against *S aureus*. The use of additional antimicrobials effective against the multitude of microorganisms that are often cultured in these patients is not associated with better outcomes than is antistaphylococcal therapy alone.[8,9]

Surgical site infections. Most patients who develop surgical site infections respond to removal of sutures and opening of the incision. Antimicrobial treatment is required if systemic signs of toxicity are present, if the associated erythema extends more than a few centimeters from the incision edge, if there is tissue necrosis, if the infection involves the muscular fascia, or if the patient has compromised immune function. The choice of antimicrobial therapy is predicated on the expected organisms, which are determined on the basis of the principles discussed above.

Necrotizing soft-tissue infections. Recommendations for the treatment of these infections are presented in **Table 5**. Some necrotizing soft-tissue infections can be associated with streptococcal toxic shock syndrome. This syndrome is caused by group A streptococci and should be treated with both clindamycin and penicillin.[2] Clindamycin has been shown to suppress toxin production and reduce cytokine production.

General treatment considerations

Many patients with complicated skin and soft-tissue infections may require surgical intervention to achieve an appropriate response. In these circumstances, antimicrobial therapy alone will not be successful.[32] Once appropriately treated, these patients should show rapid regression of infection. Patients who do not respond to initial therapy must be considered to have an undiagnosed deep infection or infection with an antimicrobial-resistant organism. In these circumstances, selection of a different agent or initiation of broader antimicrobial coverage should be considered.

Gram stain results should be checked, as they may identify unsuspected organisms. Culture and sensitivity test results also should be checked. Identification of a resistant organism should prompt a change in antibiotics. If possible, the antimicrobial spectrum should be narrowed based on the culture and sensitivity results.

SUMMARY

Skin and soft-tissue infections are common, and most are uncomplicated. The true challenge of managing these infections is to avoid delays in diagnosis and thereby prevent uncomplicated infections from progressing. The physician who encounters a skin or soft-tissue infection must respond quickly with an appropriate therapeutic plan. This can include hospitalization, prompt initiation of antimicrobial therapy, and surgical consultation. In many patients, successful treatment will require surgical intervention. The recent proliferation of community-acquired MRSA has affected the choice of antimicrobial therapy. Physicians need to be aware of these changing trends in microbial resistance to optimize care for patients with complicated skin and soft-tissue infections.

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