Cellulitis and erysipelas

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INTRODUCTION — Cellulitis and erysipelas are skin infections that develop as a result of bacterial entry via breaches in the skin barrier. The incidence is about 200 cases per 100,000 patient-years [1]. Cellulitis is observed most frequently among middle-aged individuals and older adults, while erysipelas occurs in young children and older adults [2,3].

The clinical manifestations, diagnosis, microbiology, and treatment of cellulitis and erysipelas will be reviewed here. Issues related to special forms of cellulitis are discussed separately. (See “Clinical manifestations, diagnosis, and management of diabetic infections of the lower extremities” and “Initial management of animal and human bites” and “Soft tissue infections due to dog and cat bites” and “Soft tissue infections following water exposure” and “Orbital cellulitis”.)

CLINICAL MANIFESTATIONS — Cellulitis and erysipelas manifest as areas of skin erythema, edema, and warmth. They differ in that erysipelas involves the upper dermis and superficial lymphatics, whereas cellulitis involves the deeper dermis and subcutaneous fat. As a result, erysipelas has more distinctive anatomic features than cellulitis; erysipelas lesions are raised above the level of surrounding skin, and there is a clear line of demarcation between involved and uninvolved tissue [4]. Classic descriptions of erysipelas note “butterfly” involvement of the face. Involvement of the ear (Milian's ear sign) is a distinguishing feature for erysipelas, since this region does not contain deeper dermis tissue. In addition, patients with erysipelas tend to have acute onset of symptoms with systemic manifestations including fever and chills; patients with cellulitis tend to have a more indolent course with development of localized symptoms over a few days’ time. Cellulitis may present with or without purulent drainage or exudate [5].

The lower extremities are the most common site of infection for both erysipelas and cellulitis (picture 1A-B) [2,6]. Other forms of cellulitis include periorbital cellulitis, abdominal wall cellulitis (in morbidly obese individuals), buccal cellulitis (due to Streptococcus pneumoniae and, prior to the conjugate vaccine era, Haemophilus influenzae type b) and perianal cellulitis (due to group A beta-hemolytic Streptococcus) [7,8]. (See “Orbital cellulitis”.)

Rarely, infections involving the medial third of the face (ie, the areas around the eyes and nose) can be complicated by septic cavernous thrombosis, since the veins in this region are valveless (figure 1). (See “Septic dural sinus thrombosis”.)

Additional manifestations of cellulitis and erysipelas include lymphangitis and inflammation of regional lymph nodes. Edema surrounding the hair follicles may lead to dimpling in the skin, creating an appearance reminiscent of an orange peel texture (“peau d’orange”). Vesicles, bullae, and ecchymoses or petechiae may be observed. Crepitant and gangrenous cellulitis are unusual manifestations of cellulitis due to clostridia and other anaerobes. Severe manifestations with systemic toxicity should prompt investigation for additional underlying sources of infection. (See “Epidemiology, clinical manifestations, and diagnosis of streptococcal toxic shock syndrome” and “Staphylococcal toxic shock syndrome”.)

Predisposing factors include disruption to the skin barrier as a result of trauma (such as insect bites, abrasions, penetrating wounds, or injection drug use), inflammation (such as eczema or radiation therapy), preexisting skin infection (such as impetigo or tinea pedis), varicella, and edema (due to venous insufficiency) [9,10]. Lymphatic obstruction following surgical procedures also predisposes to cellulitis. Such procedures include saphenous venectomy, breast cancer axillary node dissection, and lymph node dissection for pelvic malignancy [11-15]. Breaks in the skin between the toes (“toe web intertrigo”) are perhaps the most important potential sites for pathogen entry [9,16]. However, breaches in the skin may be small and clinically inapparent. (See “Recurrent cellulitis after saphenous venectomy for coronary artery bypass graft surgery” and “Cellulitis following pelvic lymph node dissection”.)

DIFFERENTIAL DIAGNOSIS — Rapidly progressive erythema with signs of systemic toxicity should prompt consideration of severe infection, including:

- Necrotizing fasciitis – Necrotizing fasciitis is a deep infection that results in progressive destruction of the muscle fascia. The affected area may be erythematous, swollen, warm and exquisitely tender. Pain out of proportion to exam findings may be observed. The diagnosis is established surgically with visualization of fascial planes. (See “Necrotizing soft tissue infections”.)
- Toxic shock syndrome – Toxic shock syndrome typically presents with pain that precedes physical findings. Clinical signs of soft tissue infection consist of local swelling and erythema followed by ecchymoses and sloughing of skin. Fever is common. Patients may be normotensive on presentation but subsequently become hypotensive. (See “Epidemiology, clinical manifestations, and diagnosis of streptococcal toxic shock syndrome”.)
- Gas gangrene – Gas gangrene should be suspected in the setting of fever and severe pain in an extremity, particularly in the setting of recent surgery or trauma. The presence of tissue crepitus favors clostridial infection. Gas gangrene can also be detected radiographically. (See “Clostridial myonecrosis”.)
Cellulitis must be distinguished from other infections including:

- Skin abscess – Skin abscess is a collection of pus within the dermis and deeper skin tissues; it is a tender, fluctuant, erythematous nodule that may present with surrounding cellulitic findings. (See "Skin abscesses, furuncles, and carbuncles").
- Erythema migrans – Erythema migrans is an early manifestation of Lyme disease; it consists of a region of erythema at the site of a tick bite, often with central clearing (picture 2 and picture 3). The diagnosis is established based on serologic testing, although sensitivity in early disease is low. (See "Clinical manifestations of Lyme disease in adults").
- Herpes zoster – The rash of herpes zoster begins as erythematous papules that evolve into grouped vesicles (picture 4). The rash is generally limited to one dermatome but can affect two or three neighboring dermatome. The diagnosis is established by polymerase chain reaction or direct fluorescent antibody. (See "Clinical manifestations of varicella-zoster virus infection: Herpes zoster").
- Septic arthritis – Cellulitis may overlie a septic joint. Clinical manifestations include joint pain, swelling, warmth, and limited range of motion. The diagnosis of septic arthritis is established based on synovial fluid examination. (See "Septic arthritis in adults").
- Septic bursitis – Cellulitis may precede or accompany septic bursitis. Distinguishing cellulitis with and without bursitis depends on skilled palpation. Radiographic imaging is warranted if septic bursitis is suspected. (See "Septic bursitis").
- Osteomyelitis – Osteomyelitis may underlie an area of cellulitis. It is prudent to pursue imaging for assessment of bone involvement in the setting of chronic soft tissue infection that fails to improve with appropriate antibiotic therapy. (See "Overview of osteomyelitis in adults").

Noninfectious masqueraders of cellulitis include:

- Contact dermatitis – Contact dermatitis may be distinguished from cellulitis in that the contact dermatitis lesions are pruritic but not painful. Clinical features include erythema, edema, vesicles, bullae, and oozing. The reaction is generally limited to the site of contact and is associated with burning, stinging, or pain. (See "Irritant contact dermatitis in adults").
- Acute gout – Acute gouty arthritis consists of severe pain, warmth, erythema, and swelling overlying a single joint. The diagnosis can be established by synovial fluid analysis, which should demonstrate the characteristic urate crystals of gout or the calcium pyrophosphate crystals of pseudogout. Additional clues suggestive of gout include involvement of the first metatarsophalangeal joint, prior self-limited attacks of arthritis, and presence of tophi. (See "Clinical manifestations and diagnosis of gout").
- Drug reaction – A drug reaction presents with an erythematous macular papular rash that involves the trunk and proximal extremities. It may be accompanied by pruritus, low-grade fever, and mild eosinophilia. The diagnosis is suspected in a patient receiving drug treatment who presents with a rash of recent onset. The clinical suspicion can be substantiated by histopathologic examination of a skin biopsy. (See "Exanthematous (morbilliform) drug eruption").
- Vasculitis – The morphology of cutaneous lesions of vasculitis is variable. Macular and papular lesions are characteristically nonblanchable due to the presence of extravasated erythrocytes in the dermis, which occurs as a result of damaged vessel walls. The diagnosis is established by skin biopsy. (See "Evaluation of adults with cutaneous lesions of vasculitis").
- Insect bite – An insect bite triggers an inflammatory reaction at the site of the punctured skin, which appears within minutes and consists of pruritic local erythema and edema. In some cases, a local reaction is followed by a delayed skin reaction consisting of local swelling, itching, and erythema. (See "Insect bites").

**DIAGNOSIS** — The diagnosis of cellulitis and erysipelas is based upon clinical manifestations. Cultures of blood, needle aspirations, or punch biopsies are usually not useful in the setting of mild infection [17-25]. Blood cultures are positive in less than 5 percent of cases [17]. Culture results from needle aspiration vary from ≤5 to 40 percent, while culture of punch biopsy specimens yields a pathogen in 20 to 30 percent of cases [17-29].

Cultures of blood, pus, or bullae are more useful and should be performed in patients with systemic toxicity, extensive skin involvement, underlying comorbidities (lymphedema, malignancy, neutropenia, immunodeficiency, splenectomy, diabetes), special exposures (animal bite, water-associated injury), or recurrent or persistent cellulitis [30,31]. Cultures of swabs from intact skin are not helpful and should not be performed.

Cultures obtained from patients with lower extremity cellulitis and toe web intertrigo due to tinea pedis may be useful for identification of pathogenic bacteria [16]. This was illustrated in a study of 24 patients with cellulitis; 83 percent had tinea pedis. Cultures of the interdigital spaces yielded beta-hemolytic streptococi, S. aureus, and gram-negative bacilli (85, 45, and 35 percent of cases, respectively). In addition, molecular typing of isolates from paired blood and toe web cultures in two cases demonstrated identical streptococcal strains [32].

Radiographic examination can be a useful tool for excluding occult abscess and for distinguishing cellulitis from osteomyelitis [33,34]. Radiographic examination cannot reliably distinguish cellulitis from necrotizing fascitis or gas gangrene; if there is clinical suspicion for these entities, radiographic imaging should not delay surgical intervention [35,36]. (See "Necrotizing soft tissue infections" and "Clostridial myonecrosis").
Serology may have a useful diagnostic role in patients with recurrent cellulitis. (See “Recurrent cellulitis” below.)

MICROBIOLOGY — The vast majority of cases of erysipelas are caused by beta-hemolytic streptococci [3,37–39]. The most common cellulitis pathogens are beta-hemolytic streptococci (groups A, B, C, G, and F) and S. aureus, including methicillin-resistant strains (MRSA); gram-negative aerobic bacilli are identified in a minority of cases [16,21,31,37,38,40–42]. A prospective study of nonpurulent (eg, nonculturable) cellulitis among 179 hospitalized patients found that beta-hemolytic streptococci accounted for 73 percent of cases (diagnosed by positive blood culture results or serologic testing for anti-streptolysin-O and anti-DNase-B antibodies); despite the lack of an identifiable etiology in 27 percent of cases, the overall clinical response rate to beta-lactam therapy was 96 percent [43].

Less common pathogens include H. influenzae (buccal cellulitis), clostridia and non-spor-forming anaerobes (crepitant cellulitis), pneumococcus, and meningococcus [44–50]. Cellulitis pathogens implicated in special clinical circumstances discussed in detail separately include:

- Pasteurella multocida and Capnocytophaga canimorsus (see “Soft tissue infections due to dog and cat bites” and “Initial management of animal and human bites”)
- Aeromonas hydrophila and Vibrio vulnificus (see “Soft tissue infections following water exposure”)
- S. aureus (see “Orbital cellulitis”)
- S. pneumoniae (see “Orbital cellulitis”)
- Streptococcus agalactiae (see “Cellulitis following pelvic lymph node dissection”, section on “Streptococcal sex syndrome”)
- Streptococcus iniae (see “Fever and rash in the immunocompetent patient”)
- Clostridium species (see “Clostridial myonecrosis”)
- Erysipelothrix rhitiopathiae (see “Erysipelothrix infection”)
- Cryptococcus neoformans (see “Infectious causes of fever and rash in non-HIV immunocompromised hosts”)
- Helicobacter cinaedi (see “Fever and rash in HIV-infected patients”)
- Pseudomonas aeruginosa (see “Infectious causes of fever and rash in non-HIV immunocompromised hosts” and “Clinical manifestations, diagnosis, and management of diabetic infections of the lower extremities” and “Pseudomonas aeruginosa skin, soft tissue, and bone infections”)
- Group B Streptococcus (see “Group B streptococcal infection in neonates and young infants”, section on “Other focal infection”)

TREATMENT

Nonantibiotic therapy — Management of cellulitis and erysipelas should include elevation of the affected area and treatment of underlying conditions. Elevation facilitates gravity drainage of edema and inflammatory substances. The skin should be sufficiently hydrated to avoid dryness and cracking without interdigital maceration.

Many patients with cellulitis have underlying conditions that predispose them to developing recurrent cellulitis (these include tinea pedis, lymphedema, and chronic venous insufficiency). In such patients, treatment should be directed at both the cellulitis and the predisposing condition. Patients with edema may benefit from treatment with compressive stockings and diuretic therapy. (See “Dermatophyte (tinea) infections” and “Medical management of lower extremity chronic venous disease” and “Prevention and treatment of lymphedema”)

Antibiotics — The following guidelines for empiric antimicrobial therapy should be modified as indicated in the setting of known pathogens, underlying conditions, such as diabetes, and special circumstances, such as animal bites and water exposure. Management of patients in these settings is discussed in detail separately. (See “Clinical manifestations, diagnosis, and management of diabetic infections of the lower extremities” and “Soft tissue infections due to dog and cat bites” and “Initial management of animal and human bites” and “Soft tissue infections following water exposure”)

Cellulitis — The approach to antibiotic selection for treatment of cellulitis depends on whether the clinical presentation consists of purulent or nonpurulent cellulitis. These terms, which previously have not been used routinely to categorize cellulitis, are designations within the 2011 Infectious Disease Society of America clinical practice guidelines for methicillin-resistant S. aureus (MRSA) [5]. The use of these terms in the guidelines suggests that an infection involving purulence (whether the process began as an abscess [with secondary cellulitis] or as a cellulitis [with secondary purulence]) is potentially attributable to S. aureus, which should be reflected in the choice of empirical antimicrobial therapy.

Most patients develop mild cellulitis and can be treated with oral antibiotics; patients with signs of systemic toxicity or erythema that has progressed rapidly should be treated initially with parenteral antibiotics. Attention to dosing is important, particularly in obese individuals [51]. Underdosing in obese patients, particularly those with morbid obesity and lymphedema, may result in higher rates of treatment failure.

Treatment of cellulitis for neonates usually requires hospitalization and initial parenteral therapy, except for the mildest of cases. Empiric therapy must include coverage for group B Streptococcus in addition to methicillin-resistant Staphylococcus aureus and other beta-hemolytic streptococci. Empiric parenteral therapy options include vancomycin plus either cefotaxime or gentamicin. Antibiotics that should be avoided in this age group include tetracyclines, trimethoprim-
**sulfamethoxazole**, and **ceftriaxone** (cefotaxime is preferred over ceftriaxone). Dosing is weight- and age-based (table 1). Therapy is usually administered for 7 to 10 days.

**Purulent** — Patients with purulent cellulitis (eg, cellulitis associated with purulent drainage or exudate, in the absence of a drainable abscess) should be managed with empiric therapy for infection due to MRSA, pending culture results [5]. Empiric therapy for infection due to beta-hemolytic streptococci is likely not necessary. In a study including 422 patients with purulent soft tissue infection, MRSA was the dominant organism, isolated from 59 percent of patients, followed by methicillin-susceptible *S. aureus* (MSSA; 17 percent); beta-hemolytic streptococci accounted for a much smaller proportion of these infections (2.6 percent) [52].

Options for empiric oral therapy for treatment of MRSA include (table 2):

- **Clindamycin**
- **Trimethoprim-sulfamethoxazole**
- **Tetracycline** (**doxycycline** or **minocycline**)
- **Linezolid** or **tedizolid**

The efficacy of **clindamycin** and **trimethoprim-sulfamethoxazole** (TMP-SMX) for treatment of uncomplicated skin infection may be considered comparable; this was illustrated in a randomized trial that included 524 patients with uncomplicated skin infections, including both cellulitis and abscesses (cure rates for clindamycin and TMP-SMX were 80 and 78 percent, respectively) [53].

The duration of therapy should be individualized depending on clinical response; 5 to 10 days is usually appropriate (7 to 10 days in neonates). Longer duration of therapy may be warranted in patients with severe disease [54].

The approach to parenteral therapy is discussed separately (table 3). (See "Treatment of skin and soft tissue infections due to methicillin-resistant *Staphylococcus aureus* in adults", section on "Parenteral therapy" and "Methicillin-resistant *Staphylococcus aureus* in children; Treatment of invasive infections", section on "Treatment approach").

**Nonpurulent** — Patients with nonpurulent cellulitis (eg, cellulitis with no purulent drainage or exudate and no associated abscess) should be managed with empiric therapy for infection due to beta-hemolytic streptococci and MSSA; antibiotic therapy options are summarized in the Table (table 4) [5].

This approach was illustrated in a randomized trial including 153 patients with cellulitis without abscess; cure rates were comparable among those treated with **cephalexin** (for empiric treatment of beta-hemolytic streptococci and MSSA; 82 percent) and those treated with cephalaxin and **trimethoprim-sulfamethoxazole** (for empiric MRSA coverage; 85 percent) [55].

Additional empiric coverage for MRSA is warranted in patients who do not respond to initial therapy, patients with signs of systemic illness, patients with recurrent infection in the setting of underlying predisposing conditions, and patients with a previous episode of MRSA infection. In addition, empiric coverage for MRSA should be considered in patients with risk factors for MRSA infection and in communities where the prevalence of MRSA is greater than 30 percent (table 5) [44,56-59].

Options for empiric oral therapy for treatment of both beta-hemolytic streptococci and MRSA include (table 6):

- **Clindamycin**
- **Amoxicillin combined with trimethoprim-sulfamethoxazole**
- **Amoxicillin combined with a tetracycline** (**doxycycline** or **minocycline**)
- **Linezolid** or **tedizolid**

Monotherapy with **trimethoprim-sulfamethoxazole** for treatment of nonpurulent cellulitis may be reasonable for relatively young patients with uncomplicated infection in the absence of systemic manifestations or comorbid conditions; in one study, the efficacy of trimethoprim-sulfamethoxazole for treatment of uncomplicated skin infections (including cellulitis and abscesses) was comparable to that of clindamycin [53].

The duration of therapy should be individualized depending on clinical response; 5 to 10 days is usually appropriate (7 to 10 days for neonates). Longer duration of therapy may be warranted in patients with severe disease [54].

The approach to parenteral therapy for MRSA is discussed separately. (See "Treatment of skin and soft tissue infections due to methicillin-resistant *Staphylococcus aureus* in adults", section on "Parenteral therapy" and "Methicillin-resistant *Staphylococcus aureus* in children; Treatment of invasive infections", section on "Treatment approach").

**Erysipelas** — Patients with classic manifestations of erysipelas and systemic manifestations, such as fever and chills, should be treated with parenteral therapy. Appropriate choices include **ceftriaxone** or **cefazolin** (table 7). Ceftriaxone has activity against beta-hemolytic streptococci, the cause of erysipelas in the majority of cases. In addition, once-daily dosing allows for convenient outpatient administration. Cefazolin provides coverage against streptococci as well as MSSA, which can be useful in settings where erysipelas cannot be reliably distinguished from cellulitis.
Patients with mild infection or those who have improved following initial treatment with parenteral antibiotic therapy may be treated with oral penicillin or amoxicillin (Table 7). Macrolides (particularly erythromycin) have also traditionally been used but may not be adequate therapy in areas with relatively high resistance rates among beta-hemolytic streptococci [56,60]. In the setting of beta-lactam allergy, cephalaxin (if the patient can tolerate cephalosporins), clindamycin, or linezolid may be used [56].

The duration of therapy should be individualized depending on clinical response; 5 to 10 days is usually appropriate.

**Follow-up** — Patients with cellulitis typically report symptomatic improvement within 24 to 48 hours of beginning antimicrobial therapy, although visible improvement of clinical manifestations may take up to 72 hours. Continuing extension of erythema or worsening systemic symptoms after this period of time should prompt consideration of resistant pathogens or alternative diagnoses. (See [Differential diagnosis] above.) Evaluation for deeper infection should be considered in patients with underlying conditions, such as diabetes, venous insufficiency or lymphedema, and in patients who are becoming more systemically ill.

Some patients may observe a deepening of erythema after initiating antimicrobial therapy, particularly in the setting of erysipelas. This may be due to destruction of pathogens that release enzymes, increasing local inflammation. This should not be mistaken for a failure to respond to therapy. In one study, treatment with corticosteroids (in addition to antimicrobials) did not alter the risk of relapse or recurrence but slightly reduced healing time and antibiotic duration in patients with erysipelas [61].

**RECURRENT CELLULITIS** — Management of recurrent infection can be a challenging problem. In a study of 209 cases of cellulitis, recurrences were observed in 17 percent of patients; among 143 patients with erysipelas, 29 percent had recurrent infection [10,62]. Early episodes of cellulitis cause lymphatic inflammation, and repeated infection can lead to lymphedema. Supportive care with elevation of the affected area and treatment of underlying predisposing conditions are paramount. (See [Nonantibiotic therapy] above and [Prevention and treatment of lymphedema].)

Preventive measures for reducing the spread of staphylococci may be helpful for reducing risk for recurrent skin infection and are discussed in detail separately. (See [Methicillin-resistant Staphylococcus aureus in adults: Prevention and control] and [Methicillin-resistant Staphylococcus aureus in children: Prevention and control].)

Overall, antibiotic prophylaxis for the management of recurrent cellulitis appears efficacious. In a systematic review and meta-analysis of five trials with a total of over 500 patients with at least one prior episode of cellulitis, prophylactic antibiotic use reduced the risk of subsequent cellulitis (relative risk [RR] 0.46, 95% CI 0.26-0.79) [63]. Findings from two of the included studies also demonstrated that antibiotic prophylaxis is cost-effective [64]. In a subsequent randomized trial that included 274 patients with two or more episodes of lower extremity cellulitis, penicillin (250 mg orally twice daily) nearly halved the risk of recurrence during 12 months of prophylaxis (hazard ratio 0.55; 95% CI 0.35 to 0.86; \(p = 0.01\)), but the protective effect diminished rapidly after the prophylaxis period ended [65]. A lower likelihood of response was observed among patients with a body mass index (BMI) ≥33, multiple previous episodes of cellulitis, or lymphedema of the leg. These findings warrant further investigation since patients in these categories are most likely to receive long-term prophylaxis.

Some clinicians favor serologic testing for beta-hemolytic streptococci to help guide the choice of suppressive antibiotic therapy. Assays include the anti-streptolysin O (ASO) reaction, the anti-deoxyribonuclease B test (anti-DNase B), the anti-hyaluronidase test (AHT), or the Streptozyme antibody assay [21]. Anti-DNase B and AHT responses are more reliable than the ASO response following group A streptococcal (GAS) skin infections.

For known or presumed beta-hemolytic streptococcal infection, options for prophylactic antibiotics include monthly or bimonthly intramuscular benzathine penicillin injections (1.2 million units for patients who weigh >27 kg; 600,000 units for patients who weigh ≤27 kg) or oral therapy with penicillin V (250 to 500 mg orally twice daily) [65,66]. Staphylococcal infection prophylaxis may be attempted with clindamycin (150 mg orally once daily for adults) [67]. Staphylococcal prophylaxis for recurrent cellulitis is rarely necessary in children. Suppressive therapy may be continued for several months with interval assessment for relapse. Alternatively, patients may self-initiate antibiotic therapy immediately when symptoms of infection begin and seek medical attention.

Some patients will continue to have recurrences despite antibiotic prophylaxis; in these cases, infectious diseases consultation should be obtained to determine if other measures are needed to diminish recurrences.

**INFORMATION FOR PATIENTS** — UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)
SUMMARY AND RECOMMENDATIONS

- Cellulitis and erysipelas manifest as areas of skin erythema, edema, and warmth in the absence of underlying suppurative foci. Erysipelas has more distinctive anatomic features than cellulitis; erysipelas lesions are raised above the level of surrounding skin so that a clear line of demarcation between involved and uninvolved tissue is usually present. (See 'Clinical manifestations' above.)
- Predisposing factors include disruption to the skin barrier as a result of trauma (such as penetrating wounds or injection drug use), inflammation (such as eczema or radiation therapy), preexisting skin infection (such as impetigo or tinea pedis), and edema (due to venous insufficiency). (See 'Clinical manifestations' above.)
- The diagnosis of cellulitis is based upon clinical manifestations. Cultures are necessary only in patients with systemic toxicity, extensive skin involvement, underlying comorbidities, special exposures (animal bite, water-associated injury), or recurrent or persistent cellulitis. (See 'Diagnosis' above.)
- The most common causes of cellulitis are beta-hemolytic Streptococcus (groups A, B, C, G, and F), and other pathogens include Staphylococcus aureus; gram-negative aerobic bacilli are identified in a minority of cases. Beta-hemolytic streptococci are the predominant cause of erysipelas. (See 'Microbiology' above.)
- Management of cellulitis and erysipelas should include supportive measures, such as elevation of the affected area and treatment of underlying predisposing conditions. (See 'Nonantibiotic therapy' above.)
- Most patients develop mild cellulitis and can be treated with oral antibiotics. We recommend that patients with signs of systemic toxicity or erythema that has progressed rapidly should be treated initially with parenteral antibiotics (Grade 1B). Initial parenteral antibiotics are also indicated for most neonates with cellulitis (table 1). (See 'Cellulitis'; above.)
- Patients with nonpurulent cellulitis should be managed with empiric therapy for infection due to beta-hemolytic streptococci and methicillin-resistant S. aureus (MRSA) (table 4). Patients with nonpurulent cellulitis and additional risk factors for MRSA (table 5) should be managed with empiric therapy for infection due to beta-hemolytic streptococci and methicillin-resistant S. aureus (MRSA) (table 6). (See 'Nonpurulent' above.)
- Patients with purulent cellulitis (eg, cellulitis associated with purulent drainage or exudate, in the absence of a drainable abscess) should be managed with empiric therapy for infection due to MRSA, pending culture results (table 2). (See 'Purulent' above.)
- Patients with classic manifestations of erysipelas and systemic manifestations, such as fever and chills, should be treated with parenteral therapy. Patients with mild infection or those who have improved following initial treatment with parenteral antibiotic therapy may be treated with oral therapy (table 7). (See 'Erysipelas'; above.)
- The duration of therapy should be individualized depending on clinical response; 5 to 10 days is usually appropriate. Longer duration of therapy may be warranted in patients with severe disease. (See 'Follow-up' above.)
- We suggest administration of suppressive antibiotic therapy for patients with recurrent cellulitis who have predisposing factors that cannot be alleviated (Grade 2B). (See 'Recurrent cellulitis'; above.)

REFERENCES


Erysipelas

Erysipelas of the leg

Erysipelas of the lower leg. The rash is intensely red, sharply demarcated, swollen, and indurated.
Rarely, infections involving the medial third of the face (ie, the areas around the eyes and nose) can be complicated by septic cavernous thrombosis, since the veins in this region are valveless.
Erythema migrans lesion with central clearing and a necrotic center.

Erythema migrans lesion with uniform erythema. Note that the lesion is not a perfect circle.
Herpes zoster

Grouped vesicles and underlying erythema are present in a dermatomal distribution.
Necrotizing soft tissue infections

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INTRODUCTION — Necrotizing soft tissue infections include necrotizing forms of cellulitis, myositis, and fasciitis. These infections are characterized clinically by fulminant tissue destruction, systemic signs of toxicity, and high mortality. Accurate diagnosis and appropriate treatment must include early surgical intervention and antibiotic therapy.

Several different names have been used to describe the various forms of necrotizing infections; this is related in part to naming based on clinical features rather than surgical or pathologic findings. It is important to consider the many different types of necrotizing infections described in the literature because these descriptions may provide clinical clues needed for prompt intervention and management. The lay press has referred to organisms that cause necrotizing soft tissue infections as "flesh-eating bacteria."

Issues related to necrotizing cellulitis, fasciitis, and myositis will be reviewed here. Pyomyositis and myonecrosis are discussed separately. (See "Clostridial myonecrosis" and "Pyomyositis".)

MICROBIOLOGY — Necrotizing soft tissue infections are comprised of two distinct bacteriologic entities: type I (polymicrobial infection) and type II (group A streptococcal [GAS] infection). There are also case reports of monomicrobial necrotizing soft tissue infections due to other organisms, including Haemophilus influenzae [1-3].

- In type I infection, at least one anaerobic species (most commonly Bacteroides, Clostridium, or Peptostreptococcus) is isolated in combination with one or more facultative anaerobic streptococci (other than group A) and members of the Enterobacteriaceae (eg, E. coli, Enterobacter, Klebsiella, Proteus) [4-6]. An obligate aerobe, such as P. aeruginosa, is only rarely a component of such a mixed infection. Necrotizing fasciitis of the head and neck is usually caused by mouth anaerobes, such as Fusobacteria, anaerobic streptococci, Bacteroides, and spirochetes. Fournier’s gangrene is caused by facultative organisms (E. coli, Klebsiella, enterococci), along with anaerobes (Bacteroides, Fusobacterium, Clostridium, anaerobic or microaerophilic streptococci) [7].

- In type II, necrotizing fasciitis is generally mono-microbial, most commonly caused by group A Streptococcus (also known as hemolytic streptococcal gangrene). Aeromonas hydrophila has been associated with traumatic lesions in fresh water, and Vibrio vulnificus can cause necrotizing fasciitis in association with seawater injuries (Gulf coast and South Atlantic seaboard) or among patients with cirrhosis who ingest raw oysters [8]. Group A streptococci or other beta-hemolytic streptococci are isolated alone or in combination with other species, most commonly S. aureus. In communities with relatively high prevalence of community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA) infection, this organism is also a potential cause of monomicrobial necrotizing infection [9].

An important virulence determinant of GAS, M protein, is a filamentous protein anchored to the cell membrane. M protein has antiphagocytic properties. Many M types of GAS have been associated with necrotizing fasciitis; types 1 and 3 are most common [10,11]. These strains can produce one or more of the pyrogenic exotoxins A, B, or C [12-13]. Necrotizing fasciitis caused by these strains is associated with streptococcal toxic shock syndrome in about 50 percent of cases [10,11,14]. (See "Epidemiology, clinical manifestations, and diagnosis of streptococcal toxic shock syndrome").

Group A streptococci may localize to the exact site of muscle injury due to increased surface expression of vimentin, which specifically binds the microbe. In an in vitro model, investigators demonstrated that injured skeletal muscle cells in tissue culture increased adherence of GAS twofold due to specific binding of GAS by vimentin on the surface of these cells [15].

Pyrogenic exotoxins lead to cytokine production, which may explain some of the clinical findings of necrotizing fasciitis. The exotoxins bind to the MHC class II portion of antigen presenting cells, such as macrophages. This complex can then bind to a specific V beta segment of the T cell receptor in the absence of classical antigen processing by the macrophage [16]. Thus, pyrogenic exotoxins are superantigens and cause rapid proliferation of T cells bearing specific V beta repertoire. Such stimulation of the host’s immune cells is associated with production of both monokines (tumor necrosis factor [TNF]-alpha, interleukin [IL]-1, and IL-6) and lymphokines (IL-2 and tumor necrosis factor-beta) [17]. Expression of these cytokines in vivo probably contributes to shock, tissue destruction, and organ failure [18]. (See "Group A streptococcus: Virulence factors and pathogenic mechanisms")
The possibility of an association between use of nonsteroidal antiinflammatory drugs (NSAIDs) and development or progression of streptococcal necrotizing infection has been raised [19-21]. It is unclear whether this association is attributable to inhibition of neutrophil function and augmentation of cytokine release (eg, tumor necrosis factor) or whether the association is secondary to use of NSAIDs for pain and fever following onset of infection. One review of the literature including five prospective studies demonstrated no correlation between NSAIDs and necrotizing infection [22]. In either case, NSAIDs may mask the usual signs of inflammation, thereby delaying the diagnosis.

**Necrotizing fasciitis** — There are an estimated 3.5 cases of invasive group A Streptococcus infections per 100,000 persons in the United States; necrotizing infections make up approximately 6 percent of these cases [23]. Conditions associated with necrotizing soft tissue infection include diabetes, drug use, obesity, immunosuppression, recent surgery, and traumatic wounds [4]. In the United States, there are no convincing data that suggest an increase incidence of necrotizing fasciitis; in New Zealand, the incidence increased from 0.18 to 1.68 per 100,000 per year between 1990 and 2006 [24]. In New Zealand, the prevalence was similar among different ethnic groups, but the mortality was greater among older adults and native Pacific Islanders [24]. In addition, in the United States and Scotland, mini-epidemics of necrotizing fasciitis and gas gangrene, caused by *Clostridium sordellii* and *C. novyi*, respectively, have been reported among drug abusers injecting black tar heroin subcutaneously [25,26].

Diabetes is a particularly important risk factor; several forms of necrotizing infection have been described more frequently among diabetics. These include nonclostridial anaerobic cellulitis, synergistic necrotizing cellulitis, and type I necrotizing fasciitis [5,6]. These infections occur most frequently in the lower extremities. In addition, diabetic patients are also predisposed to developing necrotizing fasciitis in the head and neck region and the perineum.

There are two bacterial forms of necrotizing fasciitis: type I and type II. (See *Microbiology* above.)

- **Type I necrotizing fasciitis** is a mixed infection caused by aerobic and anaerobic bacteria. Risk factors include diabetes, peripheral vascular disease (PVD), immune compromise, and recent surgery, including minor procedures such as circumcision in newborn infants. Patients with diabetes and/or PVD frequently have lower extremity involvement. Neonates usually have abdominal or perineal involvement.

- **Type II necrotizing fasciitis** due to group A *Streptococcus* (GAS) or other beta-hemolytic streptococci, either alone or in combination with other species, most commonly *S. aureus*. It can occur among healthy individuals with no past medical history, in any age group [6]. Predisposing factors include a history of skin injury, such as laceration or burn, blunt trauma, recent surgery, childbirth, injection drug use, and varicella infection (chickenpox) [27,30]. In cases with no clear portal of entry, the pathogenesis of infection likely consists of hematogenous translocation of GAS from the throat (asymptomatic or symptomatic pharyngitis) to a site of blunt trauma or muscle strain [31]. Traumatic injuries in the setting of fresh or seawater can predispose to necrotizing infection due to *Aeromonas hydrophila* or *Vibrio vulnificus*, respectively; the latter can also cause necrotizing infection in patients with underlying cirrhosis who ingest contaminated oysters.

During the 1990s, there was a dramatic increase in the number of invasive infections caused by GAS. In one Canadian report, the incidence of GAS necrotizing fasciitis increased from 0.085 to 0.4 per 100,000 between 1991 and 1995 [14]. Most cases were community acquired; 20 percent were nosocomial or acquired in a nursing home. Almost one-half of patients had streptococcal toxic shock syndrome; this rate is similarly noted in other studies [10,11]. (See "Epidemiology, clinical manifestations, and diagnosis of streptococcal toxic shock syndrome").

In a retrospective review of 14 adults with necrotizing fasciitis due to community-associated methicillin-resistant *S. aureus* (MRSA), risk factors for infection included injection drug use (43 percent), diabetes (21 percent), hepatitis C infection (21 percent), malignancy (7 percent), and HIV infection (7 percent) [9]. (See "Methicillin-resistant Staphylococcus aureus infection in adults: Epidemiology").

**Necrotizing myositis** — Necrotizing myositis (spontaneous gangrenous myositis) is relatively rare. In one report, only 21 cases were documented between 1900 to 1985; in a second series of over 20,000 autopsies, only four cases were found [32,33]. The infection occurs in all age groups and affects males and females equally. It may be preceded by skin abrasions, blunt trauma, or heavy exercise. Most patients are otherwise healthy; underlying conditions such as diabetes mellitus or immune deficiency do not appear to increase risk for this infection [34]. Associated mortality is high (80 to 100 percent) [34-36].

**CLINICAL MANIFESTATIONS** — Early recognition of necrotizing infection is critical; rapid progression to extensive destruction can occur, leading to systemic toxicity, limb loss, and/or death (table 1 and table 2) [11,12,31].

**Necrotizing cellulitis** — Forms of necrotizing cellulitis include anaerobic infection and Meloney’s synergistic gangrene [5,20,37-42]. Anaerobic cellulitis may be divided into two groups: clostridial anaerobic cellulitis and nonclostridial anaerobic cellulitis.

Clostridial anaerobic cellulitis is usually caused by *C. perfringens*; less frequently, it is caused by *C. septicum*. Organisms are introduced into subcutaneous tissue via trauma, surgical contamination, or spread of infection from the bowel to the perineum, abdominal wall, or lower extremities. The presence of foreign debris and/or necrotic tissue in the depths of a
wound provides a suitable anaerobic milieu for clostridial proliferation. The onset is gradual, but subsequently the process may spread rapidly [43]. Characteristic features include thin, dark, sometimes foul-smelling wound drainage (often containing fat globules) and tissue gas formation. Pain, swelling, and systemic toxicity are not prominent features, and the relative mildness helps distinguish the process from true gas gangrene. Crepitus is observed in the skin, but there is sparing of the fascia and deep muscles. Surgical exploration and debridement are required to distinguish between anaerobic cellulitis and fasciitis or myonecrosis. (See “Clostridial myonecrosis”.)

Nonclostridial anaerobic cellulitis is caused by various non-spoore forming anaerobic bacteria (eg, Bacteroides species, peptostreptococci, and others) either alone or as mixed infections with facultative organisms (coliform bacilli, various streptococci, staphylococci). The clinical features are similar to those of clostridial anaerobic cellulitis.

Melene's synergistic gangrene is a rare infection that occurs in postoperative patients. It is characterized by a slowly expanding indolent ulceration that is confined to the superficial fascia. It results from a synergistic interaction between Staphylococcus aureus and microaerophilic streptococci [37].

Necrotizing fasciitis

**Overview** — Necrotizing fasciitis is an infection of the deeper tissues that results in progressive destruction of the muscle fascia and overlying subcutaneous fat; muscle tissue is frequently spared because of its generous blood supply [39]. Infection typically spreads along the muscle fascia due to its relatively poor blood supply; initially, the overlying tissue can appear unaffected. It is this feature that makes necrotizing fasciitis difficult to diagnose without surgical intervention.

Necrotizing fasciitis is usually an acute process but rarely may follow a subacute progressive course. The affected area may be erythematous (without sharp margins), swollen, warm, shiny, and exquisitely tender [44]. Pain out of proportion to physical exam findings may be observed [12-31]. The subcutaneous tissue may be firm and indurated such that the underlying muscle groups cannot be distinctly palpated [45]. Lymphangitis and lymphadenitis are infrequent.

The process progresses rapidly over several days, with changes in skin color from red-purple to patches of blue-gray. Within three to five days after onset, skin breakdown with bullae (containing thick pink or purple fluid) and frank cutaneous necrosis may be present initially or develop with progressive infection. Measurement of compartment pressure may aid the evaluation early in the course of infection when marked pain and swelling are present without concomitant skin changes that would indicate the diagnosis [37]. Subcutaneous gas is often present in the polymicrobial form of necrotizing fasciitis, particularly in patients with diabetes [6]. (See 'Necrotizing myositis' below.)

Most cases of necrotizing fasciitis involve a single site of soft tissue infection; multifocal necrotizing fasciitis has also been described [46]. Most cases were caused by gram-positive cocci; Vibrio vulnificus may also be associated with multifocal infection. It is uncertain whether some of these cases were related to complications of the single site infection.

In advanced infection, fever, tachycardia, and systemic toxicity are generally observed, with temperature elevation in the range of 38.9° to 40.5°C (102° to 105°F). Other symptoms include malaise, myalgias, diarrhea, and anorexia. Hypotension may be present initially or develop with progressive infection.

There are two bacterial forms of necrotizing fasciitis: type I and type II. (See Microbiology above.)

**Type I** — Type I necrotizing fasciitis is a mixed infection caused by aerobic and anaerobic bacteria. Risk factors include diabetes, peripheral vascular disease (PVD), immune compromise, and recent surgery. Patients with diabetes and/or PVD frequently have lower extremity involvement. Necrotizing fasciitis in the setting of surgical wound infection is characterized by a copious drainage, dusky and friable subcutaneous tissue, and pale, devitalized fascia. (See Complications of abdominal surgical incisions.)

Type I necrotizing fasciitis can also occur in the head and neck region or in the perineum:

- Cervical necrotizing fasciitis of the neck can result from a breach in oropharynx mucous membrane integrity following surgery or instrumentation or in the setting of odontogenic infection. In one study including 45 patients with cervical necrotizing fasciitis, most were attributable to mixed aerobic and anaerobic bacteria. The majority of cases were of dental origin (78 percent); the remaining cases were of pharyngeal origin or occurred after surgery or trauma [39]. Fasciitis spread to the face (22 percent), lower neck (56 percent), and mediastinum (40 percent). In a separate study, 28 percent of patients with necrotizing fasciitis of the head and neck developed mediastinitis; factors which contributed to mediastinal involvement included prior corticosteroid use, infection by gas-producing microbes, and a pharyngeal focus of infection [47]. Cervical (head and neck) necrotizing fasciitis is usually a mixed (type I) infection. However, group A Streptococcus (S. pyogenes) can also cause monomicrobial necrotizing fasciitis. (See Type II below.)

Bacterial penetration into the fascial compartments of the head and neck region can also result in Ludwig's angina, a rapidly expanding inflammation in the submandibular and sublingual spaces. (See Deep neck space infections.)
Necrotizing infection of the male perineum, known as Fournier's gangrene, can result from a breach in the integrity of the gastrointestinal or urethral mucosa [40,41]. Infection can occur in all age groups but is most common in older men. Necrotizing infection involving the labia and perineum can also occur in females, particularly in the setting of diabetes. Fournier's gangrene begins abruptly with severe pain and may spread rapidly to the anterior abdominal wall, the gluteal muscles, and, in males, onto the scrotum and penis (picture 1). In the setting of Fournier's gangrene, early aggressive drainage or debridement is essential [40,41,48]. Affected patients may require cystostomy, colostomy, or orchietomy [46].

In the neonate, most cases of necrotizing fasciitis are attributable to infections in association with omphalitis, balanitis, mammitis, or fetal monitoring; omphalitis is the most common predisposing condition [49,50]. Involvement of the perineum has occurred after minor surgical procedures such as hernia repair or circumcision and involvement of the abdomen as a consequence of omphalitis. Most neonates with necrotizing fasciitis are full-term infants readmitted to the hospital several days to several weeks of life after an uncomplicated pregnancy and delivery. Community-associated methicillin-resistant S. aureus (MRSA) is a common pathogen in neonates with polymicrobial infection and, at times, is the sole pathogen isolated [50,51].

Synergistic necrotizing cellulitis is a variant of necrotizing fasciitis type I that involves the skin, muscle, fat, and fascia. It is usually occurs on the legs or perineum; diabetes is a known risk factor.

Type II — Type II necrotizing fasciitis is generally monomicrobial. It is typically caused by group A Streptococcus or other beta-hemolytic streptococci either alone or in combination with other pathogens, most commonly S. aureus; it has also been referred to as "streptococcal gangrene" [20]. Vibrio vulnificus and Aeromonas hydrophila can also cause necrotizing fasciitis and the clinical manifestations are as described above. (See 'Overview' above.)

Necrotizing myositis — Necrotizing myositis (also called spontaneous gangrenous myositis) is an aggressive, necrotizing infection of skeletal muscle caused by group A Streptococcus or other beta-hemolytic streptococci. It may be preceded by skin abrasions, blunt trauma, or heavy exercise [34-36]. The clinical presentation consists of fever, exquisite pain, and swelling of the affected muscle with induration. Initially, the overlying skin may be uninvolved, but later in the course erythema, warmth, petechiae, bullae, and vesicles develop.

The infection can progress over several hours to involve contiguous muscle groups and soft tissue. Onset of hypotension may occur rapidly with development of streptococcal toxic shock syndrome [52]. In many patients, hypotension and renal failure precede the cutaneous manifestations by four to eight hours [12]. (See "Epidemiology, clinical manifestations, and diagnosis of streptococcal toxic shock syndrome").

Patients with spontaneous gangrenous myositis do not have evidence of gas formation in tissue on physical or radiographic examination; this is in contrast to clostridial myonecrosis, in which gas formation is observed. (See "Clostridial myonecrosis").

Laboratory findings — Laboratory findings are generally nonspecific. Abnormalities may include leukocytosis with a marked left shift, coagulopathy, and elevations in the serum creatine kinase (CK), lactate, and creatinine concentrations [12,53-55]. These findings, together with the clinical findings described above, should prompt surgical exploration. Once the decision is made that surgical exploration is warranted, it is critical to proceed rather than delay to obtain radiographic imaging [12].

The likelihood of necrotizing soft tissue infection cannot be predicted reliably using laboratory parameters, particularly in the setting of early infection. One small retrospective study describing a series of laboratory risk indicators reported a high specificity and negative predictive value for this scoring tool [56], although subsequent data have demonstrated limited sensitivity [57,58].

DIAGNOSIS

General approach — Necrotizing infection should be considered in patients with clinical manifestations as described above. In patients with apparent skin inflammation, it is important to consider deeper, necrotizing involvement of the muscle or fascia in the setting of fever, toxicity, soft tissue involvement with severe pain (out of proportion to skin findings in some cases), crepitus, rapid progression of clinical manifestations, and elevated serum creatine kinase (CK) level. Other potential clinical clues that should raise suspicion for a necrotizing infection include firm induration or edema of the soft tissue that extends beyond the visible erythema, bullous lesions, and skin necrosis or ecchymosis [45]. Laboratory studies and blood cultures should be sent as outlined in the following sections. However, the diagnosis of necrotizing fasciitis is established surgically, with visualization of fascial planes and muscle tissue in the operating room, and surgical intervention should not be delayed while awaiting results of other testing when there is clinical suspicion for a necrotizing infection. While obtaining a frozen section tissue biopsy at the bedside may be a useful adjunct in establishing a diagnosis of necrotizing infection [59], data for the efficacy this practice are limited and false-negative results may be obtained if deep tissue is not sampled adequately.

Surgery — Surgical exploration is the only way to definitively establish the diagnosis of necrotizing infection and distinguish it from other entities (table 2). In addition, prompt surgical exploration facilitates early debridement and allows
material to be obtained for appropriate cultures. Findings on direct visualization include swollen and dull-grey appearance of the fascia, thin exude without clear punulence, and easy separation of tissue planes by blunt dissection [48].

Radiographic imaging studies can be useful to help determine whether muscle tissue is involved in some cases but are not adequate for definitive evaluation of the fascia and should not delay surgical intervention when there is crepitus on examination or clinical evidence of progressive soft tissue infection [37].

Cultures — Microbiologic diagnosis is optimally established by Gram stain and culture of deep specimens taken during surgical exploration. Blood cultures are routinely positive in patients with necrotizing myositis [34], and they are also positive in approximately 60 percent of patients with type II necrotizing fasciitis (eg, due to group A Streptococcus or other beta-hemolytic streptococci). Among patients with type I necrotizing fasciitis (eg, polymicrobial infection), the yield is lower (20 percent in one series) [6].

In the setting of polymicrobial infection, blood culture findings may not reflect all organisms involved. Aspiration of skin or bullae for Gram stain and culture may also be useful, although this approach is not as reliable for microbiologic diagnosis as deep cultures obtained at surgery.

Surgical exploration should not be delayed while awaiting results of blood cultures or skin aspirates.

Histopathology — Characteristic pathologic features of necrotizing fasciitis include extensive tissue destruction, thrombosis of blood vessels, abundant bacteria spreading along fascial planes, and infiltration of acute inflammatory cells. The relative concentrations of bacteria and neutrophils seen on histopathologic examination of resected tissue may have prognostic importance [60].

The characteristic histopathologic findings of necrotizing myositis include degeneration and necrosis of skeletal muscle fibers, infiltration of granulocytes, and numerous bacteria in areas of muscle necrosis (picture 2).

Radiographic imaging — Radiographic imaging studies can be useful to help determine whether muscle tissue is involved but should not delay surgical intervention when there is crepitus on examination or clinical evidence of progressive soft tissue infection.

Radiographic imaging studies, such as soft tissue radiographs, computed tomography (CT) scanning, and magnetic resonance imaging (MRI), are most helpful if gas is visualized in the tissue (image 1); this is seen most frequently in type I necrotizing fasciitis or gas gangrene caused by clostridia [61,62]. The most expedient radiographic approach to assess for the presence of gas in the fascial planes is noncontrast CT examination; MRI is not as useful as CT to detect this finding. In addition, MRI can be overly sensitive; it tends to overestimate deep tissue involvement and therefore cannot be used to reliably distinguish between necrotizing cellulitis and deeper infection [63]. Ultrasound is useful to detect localized abscesses but has not been well studied in necrotizing fasciitis.

The presence of gas in the fascial planes is a highly specific finding but not very sensitive [4]. More often, imaging studies demonstrate soft tissue swelling, which may also be seen in the setting of trauma or following surgery. In such cases, the diagnosis of necrotizing fasciitis or myonecrosis can be established only by surgical exploration.

Differential diagnosis — Items included in the differential diagnosis are summarized in the Table (table 1 and table 2). In addition to soft tissue infection, other possible diagnoses include deep venous thrombosis, septic arthritis, warfarin-induced skin necrosis, brown recluse spider bite, gangrene with secondary infection, and caustic destruction of fat and muscle due to street drug krokodil [64]. (See "Acute opioid intoxication in adults", section on "Opioid adulterants, including krokodil").

Distinguishing necrotizing myositis (spontaneous gangrenous myositis) from necrotizing fasciitis may be difficult, as skeletal muscle and fascia are involved in both syndromes [12,31,36]. Necrotizing myositis primarily involves skeletal muscle, whereas necrotizing fasciitis primarily involves fascia. The development of anesthesia may precede the appearance of skin necrosis and provide a clue to the presence of necrotizing fasciitis [37].

Necrotizing myositis may also be confused with pyomyositis. These differ in that pyomyositis is characterized by abscess formation in skeletal muscle rather than gangrenous necrosis. In addition, pyomyositis is usually caused by Staphylococcus aureus and is generally associated with less systemic toxicity. (See "Pyomyositis").

TREATMENT — Treatment of necrotizing infection consists of early and aggressive surgical exploration and debridement of necrotic tissue, together with broad spectrum empiric antibiotic therapy and hemodynamic support. Surgery is indicated in the setting of severe pain, toxicity, fever, and elevated serum creatine kinase (CK) level, with or without radiographic evidence of fasciitis. Use of antibiotic therapy without debridement is associated with a mortality rate approaching 100 percent [4]. Hemodynamic instability may require aggressive supportive care with fluids and vasopressors. (See "Evaluation and management of severe sepsis and septic shock in adults").

Surgery — Necrotizing infections of the skin and fascia are surgical emergencies. Radiographic imaging studies should not delay surgical intervention when there is crepitus on examination or clinical evidence of progressive soft tissue infection.

The goal of operative management is to perform aggressive debridement of all necrotic tissue until healthy, viable (bleeding) tissue is reached. Tissue obtained in the operating room should be sent for Gram stain and culture. Subsequently, the wound is covered with a sterile dressing, reevaluated in the operating room approximately 24 hours later,
and aggressively debrided again if necrotic tissue is present [44]. The wound is closed after all necrotic tissue is completely debrided. In some cases, allografting or myocutaneous tissue reconstruction is required to cover the defect. For severe necrotizing infections involving the digits or extremities, amputation may be required to control the infection [4]. Issues related to reconstructive procedures are discussed separately. (See “Principles of grafts and flaps for reconstructive surgery.”)

**Antibiotic therapy** — The optimal approach to empiric antibiotic therapy for necrotizing infection is uncertain; data are limited since most clinical trials exclude such patients. In general, empiric treatment of necrotizing infection should consist of broad-spectrum antimicrobial therapy, including activity against gram-positive, gram-negative, and anaerobic organisms; special consideration for group A Streptococcus (GAS) and Clostridium species should be taken [4].

Acceptable regimens include administration of:

- A carbapenem or beta-lactam-beta-lactamase inhibitor, plus clindamycin (dosed at 600 to 900 mg intravenously every eight hours in adults or 40 mg/kg per day divided every eight hours in neonates and children) for its antitoxin effects against toxin-elaborating strains of streptococci and staphylococci [31, 65-70], plus
- An agent with activity against methicillin-resistant *S. aureus* (MRSA; such as vancomycin, daptomycin, or linezolid (table 3). In neonates and children, vancomycin (15 mg/kg/dose every six to eight hours) is the usual empiric antibiotic for MRSA; the six-hour dosing interval is employed for sicker children.

For patients who have particular exposures that may suggest infections with specific organisms, such as trauma in fresh water (*Aeromonas*) or sea water (*V. vulnificus*), it is appropriate to ensure that empiric therapy includes antimicrobial agents active against such organisms. (See “Aeromonas infections”, section on ‘Therapy’ and “Vibrio vulnificus infections”, section on ‘Therapy’ and “Soft tissue infections following water exposure.”)

Options for carbapenems include imipenem, meropenem, or ertapenem. Meropenem (20 mg/kg per dose every eight hours) is the appropriate carbapenem for use in neonates with a postnatal age >7 days and children. Options for beta-lactam-beta-lactamase inhibitors include piperacillin-tazobactam, ampicillin-sulbactam, or ticarcillin-clavulanate. Patients with hypersensitivity to these agents may be treated either with an aminoglycoside or a fluoroquinolone, plus metronidazole.

Antibiotic treatment should be tailored to Gram stain, culture, and sensitivity results when available. In the setting of known group A streptococcal or other beta-hemolytic streptococcal infection, treatment may be narrowed to the combination of penicillin (4 million units intravenously every four hours in adults >60 kg in weight and with normal renal function or 300,000 units/kg per day divided every six hours in children) and clindamycin (600 to 900 mg intravenously every eight hours in adults or 40 mg/kg per day divided every eight hours in neonates and children) [31]. Therapy against MRSA may be discontinued after methicillin-resistant staphylococcal infection has been excluded.

The optimal duration of antibiotic treatment has not been defined in clinical trials. Antibiotics should be continued until no further debridements are needed and the patient’s hemodynamic status has normalized; this duration must be tailored to individual patient circumstances.

**Intravenous immune globulin** — Intravenous immune globulin (IVIG) contains neutralizing antibodies against some streptococcal superantigens and clostridial toxins [71, 72]. Use of high-dose IVIG (up to 2g/kg) appears to be beneficial in severe GAS infections, although efficacy data are not definitive [42, 73-76]. (See “Treatment of streptococcal toxic shock syndrome”, section on ‘Intravenous immune globulin’ and “General principles in the use of immune globulin.”)

In a controlled trial among 21 adults with streptococcal toxic shock syndrome with or without necrotizing fasciitis, patients who received placebo had 3.6-fold higher mortality than patients who received IVIG; statistical significance was not reached (presumably because of the small sample size) [75]. IVIG dosing was 1 g/kg (day one) and 0.5 g/kg (days two and three). In an observational study comparing 30-day survival among 53 patients with streptococcal toxic shock syndrome, 30-day survival was higher among those who received IVIG than those who did not (67 versus 34 percent; p = 0.02) [73]. A greater number of patients in the IVIG group received clindamycin and were more likely to have had surgical intervention.

**Hyperbaric oxygen** — The utility of hyperbaric oxygen treatment in the management of necrotizing fasciitis is discussed separately. (See “Hyperbaric oxygen therapy”, section on ‘Infection’.)

**Postexposure prophylaxis** — Group A *Streptococcus* is a highly contagious organism; it has caused epidemics of pharyngitis and scarlet fever in schools, rheumatic fever in military recruits, and surgical wound infections in hospitalized patients. Close contacts of a case of type II necrotizing fasciitis have a high likelihood of becoming colonized with a virulent strain. The risk of developing a secondary case of fulminant necrotizing fasciitis or toxic shock syndrome is very low but higher than for the general population [77, 78].

The role of postexposure prophylaxis has not been studied, and the optimal approach is uncertain [79]. For highly susceptible individuals (such as immunocompromised individuals or patients with recent surgery) who are close household contacts of a patient with type II necrotizing fasciitis, administration of prophylaxis with penicillin (250 mg orally four times
daily for 24 to 48 hours) is reasonable. The goal is reduction in likelihood of a secondary infection rather than treatment of established infection.

OUTCOME — Necrotizing infection is associated with considerable mortality, even with optimal therapy. The mortality rates in different studies have included 21 percent in type I necrotizing fasciitis [6], 14 to 34 percent in type II necrotizing fasciitis (in which streptococcal toxic shock syndrome is commonly associated with mortality) [10,12,14], 22 percent in patients with cervical necrotizing fasciitis [39], and 22 to 40 percent in patients with Fournier's gangrene [40,41,80]. In a review of 66 cases of neonatal necrotizing fasciitis, the mortality rate was 59 percent [49].

In one retrospective study of 166 patients with necrotizing soft tissue infections, the overall mortality rate was 17 percent [81]. Predictors of mortality after multivariate analysis included white blood cell count >30,000/microL, serum creatinine >2.0 mg/dL (177 mmol/L), clostridial infection, and the presence of heart disease on admission. In a second retrospective study from Taiwan, predictors of mortality were cirrhosis of the liver, soft tissue air, Aeromonas infection, age >60 years, band neutrophils >10 percent, activated partial thromboplastin time >60 seconds, bacteremia, and creatinine >2 mg/dL [82]. The length of time from admission to surgery did not impact mortality, probably because surgical treatment in all patients was instituted within 24 hours of admission. In earlier studies, a delay in surgery for more than 24 hours was a risk factor for mortality [6]. In general, infection involving the head, neck, thorax, and abdomen are associated with greater mortality due to difficulty in surgical debridement.

Among patients with necrotizing fasciitis, the mortality rate is higher in patients with streptococcal toxic shock syndrome. This was illustrated in a series of 62 patients with group A streptococcal necrotizing fasciitis; 52 percent also had streptococcal toxic shock syndrome [10]. The patients with toxic shock syndrome had a significantly higher mortality rate (28 versus 8 percent).

Further study is needed to understand the impact of other factors that likely contribute to mortality, including the duration of time from onset of infection to definitive treatment; the type, extent, and adequacy of surgical debridement; and infection of the head and neck, thorax, and abdomen (which are more complex in terms of surgical debridement).

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Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

SUMMARY AND RECOMMENDATIONS

- Necrotizing soft tissue infections are characterized clinically by fulminant tissue destruction, systemic signs of toxicity, and high mortality rate. Conditions associated with necrotizing infection include diabetes, drug use, obesity, immunosuppression, recent surgery, and traumatic wounds. (See ‘Introduction’ above and ‘Epidemiology’ above.)
- There are two bacteriologic categories of necrotizing soft tissue infections: type I (polymicrobial infection) and type II (group A or other beta-hemolytic streptococcal infection). In type I infection, at least one anaerobic species is isolated in combination with one or more facultative anaerobic streptococci (other than group A) and members of the Enterobacteriaceae. In type II infection, group A streptococci or other beta-hemolytic streptococci are isolated alone or in combination with other species, most commonly S. aureus. (See ‘Microbiology’ above.)
- Necrotizing cellulitis presents with thin, dark wound drainage and gas formation in the skin (but sparing of the fascia and deep muscles). The onset is gradual, but subsequently the process may spread rapidly. Pain, swelling, and systemic toxicity are not prominent features; absence of these findings helps distinguish the process from true gas gangrene. Surgical exploration and debridement are required to distinguish between anaerobic cellulitis and fasciitis or myonecrosis. (See ‘Necrotizing cellulitis’ above.)
- Necrotizing fasciitis is a deep infection of the subcutaneous tissue that results in progressive destruction of fascia and fat. The affected area is usually erythematous (without sharp margins), swollen, warm, shiny, and exquisitely tender. The process progresses rapidly over several days, with changes in skin color from red-purple to patches of blue-gray. Skin breakdown with bullae (containing thick pink or purple fluid) and frank cutaneous gangrene may be observed within three to five days. The development of anesthiesia may precede the appearance of skin necrosis and provide a clue that the process is necrotizing fasciitis rather than cellulitis. In advanced infection, high fever and systemic toxicity are generally observed. (See ‘Necrotizing fasciitis’ above.)
- Necrotizing myositis (also called spontaneous gangrenous myositis) is an aggressive infection of skeletal muscle. The clinical presentation consists of fever, exquisite pain, and swelling of the affected muscle with induration. Initially, the overlying skin may be uninvolved, but subsequently erythema, warmth, petechiae, bullae, and vesicles may
develop. The infection can progress over several hours to involve contiguous muscle groups and soft tissue. Onset of hypotension may occur rapidly with development of streptococcal toxic shock syndrome. (See *Necrotizing myositis* above.)

- **Surgical exploration is the only way to definitively establish the diagnosis of necrotizing fasciitis and distinguish it from other entities. In addition, prompt surgical exploration facilitates early debridement and allows material to be obtained for appropriate cultures. Radiographic imaging studies can be useful to help determine whether muscle tissue is involved but should not delay surgical intervention when there is crepitus on examination or clinical evidence of progressive soft tissue infection. (See *Diagnosis* above and *Radiographic imaging* above.)**

- **Treatment of necrotizing infection consists of early and aggressive surgical exploration and debridement of necrotic tissue, together with broad spectrum empiric antibiotic therapy and hemodynamic support. Acceptable antibiotic regimens include administration of a carbapenem or beta-lactam-beta-lactamase inhibitor, together with clindamycin (600 to 900 mg intravenously every eight hours for adults and 40 mg/kg per day divided every eight hours in children), as well as an agent with activity against methicillin-resistant *S. aureus* (MRSA) (table 3). Antibiotic treatment should be tailored to Gram stain, culture, and sensitivity results when available. (See *Treatment* above and *Antibiotic therapy* above.)**

- **Intravenous immune globulin (IVIG) contains neutralizing antibodies against some streptococcal superantigens and clostridial toxins. Data on the efficacy of this agent in the setting of necrotizing infection are limited. For cases of necrotizing fasciitis due to group A *Streptococcus* complicated by streptococcal toxic shock syndrome, we suggest administration of IVIG (Grade 2C). (See *Intravenous immune globulin* above.)**

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**REFERENCES**


INTRODUCTION — Diabetic foot infections are associated with substantial morbidity and mortality [1]. Important risk factors for development of diabetic foot infections include neuropathy, peripheral vascular disease, and poor glycemic control. In the setting of sensory neuropathy, there is diminished perception of pain and temperature; thus, many patients are slow to recognize the presence of an injury to their feet. Autonomic neuropathy can cause diminished sweat secretion resulting in dry, cracked skin that facilitates the entry of microorganisms to the deeper skin structures. In addition, motor neuropathy can lead to foot deformities, which lead to pressure-induced soft tissue damage. Peripheral artery disease can impair blood flow necessary for healing of ulcers and infections. Hyperglycemia impairs neutrophil function and reduces host defenses. Trauma in patients with one or more of these risk factors precipitates development of wounds that can be slow to heal and predispose to secondary infection.

The microbiology, clinical evaluation, diagnosis, and management of diabetic foot infections will be reviewed here. The general evaluation of the diabetic foot and management of uninfected diabetic foot lesions are discussed separately. (See "Evaluation of the diabetic foot" and "Management of diabetic foot lesions").

OVERVIEW OF APPROACH TO THE PATIENT — In 2012, the Infectious Disease Society of America updated guidelines on the diagnosis and management of diabetic foot infections, which were originally published in 2004 [2]. Practical

Clinical manifestations, diagnosis, and management of diabetic infections of the lower extremities

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guidelines are also published regularly by the International Working Group on the Diabetic Foot [3]. The information reviewed in this topic is largely consistent with these guidelines.

The evaluation of a patient with a diabetic foot infection involves three key steps: 1) determining the extent and severity of infection, 2) identifying underlying factors that predispose to and promote infection, and 3) assessing the microbial etiology.

The clinical history should focus on the details related to recent trauma, the duration of the current lesion(s), associated systemic symptoms, and prior treatment, if any. Mechanical factors that may predispose to the formation of an ulcer should be noted, and the history of blood glucose control should be assessed. Evidence of systemic toxicity should also be carefully noted.

Clinical examination should note the location of the lesions, extent of infection (eg, involving skin, subcutaneous tissue, muscles, tendons and/or bone) and whether bone is grossly visible or palpable by probing. Although osteomyelitis is highly likely if bone is visible, it may be present in the absence of such findings. (See "Diagnosis of underlying osteomyelitis" below.)

Clinical examination should also include a neurologic evaluation that documents the extent of sensory loss as well as a vascular evaluation of the presence and severity of arterial and/or venous insufficiency. (See "Evaluation of the diabetic foot".)

Laboratory evaluation should include complete blood count as well as measurement of blood glucose, electrolytes, and renal function. Baseline and subsequent inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) can be useful for monitoring response to therapy [4]. Some [5,6] but not all studies [7] have suggested that procalcitonin (PCT), a novel inflammatory marker, may also be useful if laboratory facilities that test this substance are locally available; further investigation is needed to determine the clinical utility of this assay. (See "Diagnosis of underlying osteomyelitis" below.)

Initial evaluation should include conventional radiographs to evaluate for bony deformity, foreign bodies, and gas in the soft tissue. In select cases, magnetic resonance imaging (MRI) can be performed to better evaluate for soft tissue abnormalities and osteomyelitis. (See "Osteomyelitis" below and "Approach to imaging modalities in the setting of suspected osteomyelitis").

Aerobic and anaerobic cultures of deep tissue or bone biopsies should be obtained at the time of debridement if deep tissue infection or osteomyelitis is suspected. (See "Obtaining samples for culture" below.)

If surgical intervention is warranted for management of infection, formal neurological and/or vascular evaluation is important for determining the extent of surgical intervention. (See "Surgery" below and "Evaluation of the diabetic foot").

MICROBIOLOGY — Most diabetic foot infections are polymicrobial, with up to five to seven different specific organisms often involved. The microbiology of diabetic foot wounds is variable depending on the extent of involvement [4,8-10]:

- Superficial diabetic foot infections (including cellulitis and infected ulcers in antibiotic-naïve individuals) are likely due to aerobic gram-positive cocci (including S. aureus, S. agalactiae, S. pyogenes, and coagulase-negative staphylococci).
- Ulcers that are deep, chronically infected, and/or previously treated with antibiotics are more likely to be polymicrobial. Such wounds may involve the above organisms in addition to enterococci, Enterobacteriaceae, Pseudomonas aeruginosa, and anaerobes.
- Wounds with extensive local inflammation, necrosis, malodorous drainage, or gangrene with signs of systemic toxicity should be presumed to have anaerobic organisms in addition to the above pathogens. Potential pathogens include anaerobic streptococci, Bacteroides species, and Clostridium species [11-15].

Risk of specific organisms

Resistant Staphylococcus aureus — Methicillin-resistant S. aureus (MRSA) is a common pathogen in diabetic foot infections, particularly in those who have had previous MRSA infections or known colonization. Other risk factors for MRSA infection include prior antibiotic use, previous hospitalization, and residence in a long-term care facility. (See "Methicillin-resistant Staphylococcus aureus infection in adults: Epidemiology", section on "Risk factors").

It is also important to note that diabetic patients with chronic foot wounds who receive repeated and prolonged courses of antibiotics represent an important risk group for development of vancomycin-intermediate Staphylococcus aureus infections. (See "Vancomycin-intermediate and vancomycin-resistant Staphylococcus aureus infections").

Pseudomonas aeruginosa — P. aeruginosa is a particularly prevalent organism in diabetic foot infections reported from regions with warm climates. As an example, in a study of 434 patients with infected diabetic foot ulcers in Northern India, P. aeruginosa was the most common isolate, found in 20 percent of initial cultures [16]. Macerated ulcers, foot soaking, and other exposure to water or moist environments also likely increases the risk of involvement with P. aeruginosa. However, in temperate climates and in the absence of the preceding findings and exposures, P. aeruginosa is not a particularly common pathogen. Furthermore, its role as a pathogen in routine clinical practice is often hard to assess. As an example, when P.
aeruginosa was isolated from participants of clinical studies of diabetic foot infections, most patients improved on antibiotic regimens that did not cover Pseudomonas, suggesting that it was not the primary pathogenic organism.\cite{17,18}

**Resistant enteric gram-negative rods** — Gram-negative bacilli that express an extended-spectrum beta-lactamase (ESBL) are increasing in prevalence worldwide. These pathogens are more common in patients with prolonged hospital stays, prolonged catheterization, prior antibiotic use, or residence in a long-term care facility (see "Extended-spectrum beta-lactamases", section on 'Epidemiology'). The involvement of ESBL-producing organisms in diabetic foot infections in particular is also increasingly reported.\cite{19,20}

**CLINICAL MANIFESTATIONS** — Diabetic foot infections can develop as a result of neuropathic or ischemic ulcers, traumatic wounds, skin cracks or fissures, or other defects in the skin of the foot or nail beds (paronychia).\cite{2,21} Thus, infection can present as localized superficial skin involvement at the site of a preexisting lesion or as infection of the skin or deeper skin structures that has spread beyond the site of local trauma. Such infections can subsequently extend to joints, bones, and the systemic circulation.

Diabetic foot infections are often accompanied by the cardinal manifestations of inflammation (erythema, warmth, swelling, and tenderness) and/or the presence of pus in an ulcer or sinus tract.\cite{8} However, these local signs of infection may not be evident in certain cases. Infections may not manifest with warmth and erythema in the setting of severe ischemia. Diabetics with sensory neuropathy may have diminished sensation in the involved area and therefore may not complain of tenderness nor, in some cases, even realize that infection is present. In such instances, infection may progress to involve deeper tissues before the patient seeks clinical attention.

Other local signs that may be present in diabetic foot infections but are nonspecific include nonpurulent drainage, friable or discolored granulation tissue, and undermining of wound edges.\cite{2}

Cutaneous bullae, soft tissue gas, skin discoloration, or a foul odor may occur in necrotizing infections. Findings of gangrene, severe ischemia, or tissue necrosis may denote the presence of a limb-threatening infection.

Systemic signs such as fever, chills, hypotension, and tachycardia may accompany local signs of infection, and their presence indicates an increased severity of infection.\cite{21}

**Osteomyelitis** — Osteomyelitis can occur in the setting of a diabetic foot wound with or without evidence of local soft tissue infection. Several clinical features are associated with the presence of underlying osteomyelitis in patients with diabetic foot ulcers, including ulcer size $\geq 2$ cm\(^2\) and depth allowing visibly exposed bone or ability to probe to bone.\cite{22-25} The presence of a "sausage" toe, with erythema and nonpitting edema that obliterates the normal contour of the digit, has been associated with underlying osteomyelitis in diabetic patients, but the frequency of this finding is not known.\cite{26}

Although not specific or highly sensitive, the erythrocyte sedimentation rate (ESR) may be useful in evaluating whether osteomyelitis is present. The finding of an ESR of 70 or greater increases the clinical probability that osteomyelitis is present.\cite{24}

On plain radiographs, findings characteristic of osteomyelitis include cortical erosion, periosteal reaction, mixed lucency, and sclerosis.\cite{2,24} There is often also evidence of soft tissue swelling. However, radiographs may be normal or have only subtle non-specific findings early in infection. Magnetic resonance imaging (MRI) findings of osteomyelitis include cortical destruction, bone marrow edema, and soft tissue inflammation.\cite{23,28}

**DIAGNOSIS** — The diagnosis of a diabetic foot infection is primarily based on suggestive clinical manifestations. The presence of two or more features of inflammation (erythema, warmth, tenderness, swelling, induration and purulent secretions) can establish the diagnosis.\cite{2,27} (See 'Clinical manifestations' above.)

As many diabetic foot wounds are colonized by bacteria, the presence of microbial growth from a wound culture in the setting of diabetic foot ulcers, the following factors increase the likelihood of osteomyelitis:\cite{24,25}:

- Grossly visible bone or ability to probe to bone
- Ulcer size larger than 2 cm\(^2\)
- Ulcer duration longer than one to two weeks
If bone is grossly visible, supportive radiographic findings may not be necessary to make a diagnosis of osteomyelitis. However, for diabetic patients with one or more of the other above factors, a conventional radiograph with consistent changes can be helpful in making the diagnosis of osteomyelitis and providing a baseline image useful for subsequent management decisions. If the radiograph is indeterminate or normal and the diagnosis remains uncertain, such patients should undergo magnetic resonance imaging (MRI), which is highly sensitive and specific for osteomyelitis and superior to radiographs, three-phase bone scans, and white blood cell scans. (See ‘Osteomyelitis’ above.)

In cases of diagnostic uncertainty based on clinical or radiographic features, failure of empiric antibiotic therapy, planned hardware placement in potentially infected bone, and mid- or hindfoot lesions that could lead to high-level amputations if inadequately treated, obtaining a bone sample to establish diagnosis is recommended. Culture of such bone biopsy specimens is also important for identifying the causative organisms and their susceptibilities in order to guide antimicrobial therapy.

A detailed approach to the diagnosis of osteomyelitis in general is outlined separately. (See “Overview of osteomyelitis in adults” and “Approach to imaging modalities in the setting of suspected osteomyelitis”.)

DIFFERENTIAL DIAGNOSIS — Other processes that lead to inflammatory changes in the skin of the lower extremities can mimic an infection. These include trauma, crystal-associated arthritis, acute Charcot arthropathy, fracture, thrombosis, and venous stasis. Usually, infection can be distinguished from these based on history, exam, and imaging findings. However, infection may co-exist with other inflammatory processes, and empiric antimicrobial therapy may be warranted in some cases when the diagnosis is unclear. (See “Clinical manifestations and diagnosis of gout” and “Diabetic neuropathic arthropathy” and “Approach to the diagnosis and therapy of lower extremity deep vein thrombosis” and “Clinical manifestations of lower extremity chronic venous disease”.)

DETERMINING SEVERITY OF INFECTION — Assessment of the severity of diabetic foot infections is important for prognosis and to assist with management decisions (eg, need for hospitalization, surgical evaluation, or parental versus oral antibiotic therapy). In its 2004 guidelines on the diagnosis and treatment of diabetic foot infections, the Infectious Diseases Society of America (IDSA) first outlined a clinical classification scheme to define levels of severity (table 1). Briefly, it classifies diabetic foot changes as uninfected, mild, moderate, and severe based on the extent of inflammatory findings, the tissue depth involved, and the presence of signs of systemic toxicity. The International Working Group on the Diabetic Foot published a nearly identical classification system in 2012.

The prognostic value of such classification schema was assessed in a longitudinal study of 1666 persons with diabetes; there was a trend toward increased amputation risk among patients with more severe infections.

MANAGEMENT — Management of diabetic foot infections requires attentive wound management, good nutrition, appropriate antimicrobial therapy, glycemic control, and fluid and electrolyte balance. Although severe infections warrant hospitalization for urgent surgical consultation, antimicrobial administration, and medical stabilization, most mild infections and many moderate infections can be managed in the outpatient setting with close follow-up. Hospitalization may be needed for mild or moderate infections if the patient cannot manage glycemic control at home, is unable to obtain or comply with proper wound care or offloading, needs parenteral antibiotics and is unsuitable for outpatient parenteral antimicrobial therapy, or needs more urgent diagnostic studies or surgical consultation.

Several studies have reported improved outcomes with a multidisciplinary approach to diabetic foot infections. This includes involvement of specialists in wound care, infectious diseases, endocrinology, and surgery.

Wound management — Local wound care for diabetic foot infections typically includes debridement of callus and necrotic tissue, wound cleansing, and relief of pressure on the ulcer. Sharp debridement, with the use of a scalpel or scissors to shear off necrotic tissue, is the preferred method to remove callus and nonviable tissue. Such debridement promotes wound healing and removes pathogens that are present in nonviable tissues. However, enzymatic debridement may be preferable in patients with significant vascular compromise that might impede the ability to heal new wounds created by sharp debridement. As a general rule, surgical intervention is needed for patients with extensive infection of subcutaneous or deeper structures. (See “Management of diabetic foot lesions”, section on ‘Method of debridement’ and ‘Surgery’ below.)

The purpose of wound dressing is to absorb exudate and create a moist environment to promote healing. A wide array of dressing and wound healing products for ulcer management has been developed. These products include enzymes, gels, hydrocolloids, honey and antiseptics containing iodine or silver salts. However, the efficacy of these agents has not been evaluated or compared in carefully designed studies. Avoidance of weight bearing is generally more important than the specific type of wound dressing or ointment applied. (See “Management of diabetic foot lesions”, section on ‘Local wound care’.)

Off-loading the pressure on the diabetic foot wound is essential to wound care. Various devices to relieve pressure on the foot are available, including casts and special shoes. The choice of device should be based on the wound location, the

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severity of infection, and the presence of peripheral arterial disease. (See "Management of diabetic foot lesions", section on 'Mechanical off-loading'.)

**Obtaining samples for culture** — Because microorganisms often colonize lower extremity wounds regardless of the presence of a true infection, cultures should be performed only in selected patients. If the clinical suspicion for infection is low, samples from the wound should not be submitted for culture. In patients with mild infection (table 1) in whom there is low suspicion for resistant organisms (eg, no recent antibiotic course), wound culture is often not necessary. However, wound culture is often helpful in cases of moderate or severe infection (table 1) and when the concern for multidrug-resistant organisms is high. Ideally, samples for culture should be obtained prior to the initiation of empiric antibiotics. However, in cases of systemic toxicity or limb-threatening infections, antibiotic therapy should not be withheld before surgical cultures are obtained.

The preferred clinical specimens for reliable culture include aspirate from an abscess or curettage from the ulcer base following superficial debridement of necrotic tissue. Organisms cultured from superficial swabs are not reliable for predicting the pathogens responsible for deeper infection [35-38]. (See "Overview of osteomyelitis in adults").

In the setting of osteomyelitis, bone biopsy is the preferred method of sample collection for culture. If performed percutaneously, sampling through uninvolved tissue under radiographic guidance is preferred. Although sinus tract cultures may be of some use for prediction of osteomyelitis if Staphylococcus aureus or Salmonella species are identified, in general, such cultures are not worthwhile [39-40]. (See 'Diagnosis of underlying osteomyelitis' above and 'Overview of osteomyelitis in adults', section on 'Bone biopsy'.)

Samples should be sent for both aerobic and anaerobic bacterial cultures.

**Surgery** — Consultation with a surgeon with experience in diabetic foot infections is important for cases of severe infections and in most cases of moderate infections. Surgical debridement is required for cure of infections complicated by abscess, extensive bone or joint involvement, crepitus, necrosis, gangrene or necrotizing fasciitis and is important for source control in patients with severe sepsis [24,41,42]. The utility of early surgical debridement was illustrated in a retrospective review of 112 diabetic patients with severe foot infections [41]. Those patients who underwent surgical intervention at the time of presentation had a significantly lower rate of above-ankle amputation than those who received three days of intravenous antimicrobial therapy prior to surgery.

In addition to surgical debridement, revascularization (via angioplasty or bypass grafting) and/or amputation may be necessary. Determination of the extent of surgical intervention required should be guided by vascular evaluation [2,21]. (See "Management of diabetic foot lesions", section on 'Revascularization' and "Lower extremity amputation", section on 'Indications for amputation' and "Techniques for lower extremity amputation").

**Antimicrobial therapy** — Empiric antibiotic therapy should be selected based on the severity of infection and the likelihood of involvement of resistant organisms. (See 'Determining severity of infection' above and 'Microbiology' above.)

Subsequent antibiotic therapy should be tailored to culture and susceptibility results. However, it is not always necessary to cover all microorganisms isolated from cultures [4].

Patients with ulcers that are not infected should not receive antibiotic therapy [43,44]. However, such patients often benefit from local wound care and measures that reduce the pressure at the site of ulceration.

Our treatment approach outlined below is consistent with the Infectious Diseases Society of America (IDSA) guidelines on the diagnosis and treatment of diabetic foot infections and is based on their classification scheme for severity of infection (table 1) [2,4]. (See 'Determining severity of infection' above.)

In general, the limited data on antibiotic therapy of diabetic foot infections do not allow comparison of outcomes of different regimens [2,27]. On the basis of the available observational studies and randomized trials, no single drug or combination appears to be superior to others [45]. In a systematic review of 12 studies comparing antibiotic regimens for lower extremity skin and soft-tissue infections in diabetic patients, reported clinical cure rates ranged from 48 to 90 percent [46]. None of the studies demonstrated a significant benefit for any specific antibiotic agent.

**Empiric therapy**

**Mild infection** — Mild diabetic foot infections can be treated with outpatient oral antimicrobial therapy. Empiric therapy of patients with mild infections should include activity against skin flora including streptococci and Staphylococcus aureus. Agents with activity against methicillin-resistant Staphylococcus aureus (MRSA) should be used in patients with purulent infections and those at risk for MRSA infection (see 'Resistant Staphylococcus aureus' above). Appropriate agents are outlined in the table (table 2).

Patients who fail to respond to treatment with agents active against streptococci and methicillin-susceptible S. aureus should receive extended antimicrobial coverage to include activity against MRSA, aerobic gram-negative bacilli, and anaerobes (table 2).

**Moderate infection** — Empiric therapy of deep ulcers with extension to fascia should include activity against streptococci, Staphylococcus aureus (and MRSA if risk factors are present), aerobic gram-negative bacilli and anaerobes and can be
administered orally in many cases. Appropriate regimens are outlined in the table (table 2). Patients presenting with extensive infections that involve deep tissues should receive empiric parenteral therapy with activity against the above pathogens (table 3). Empiric coverage for Pseudomonas aeruginosa may not always be necessary unless the patient has particular risk for involvement with this organism, such as a macerated wound or one with significant water exposure. (See "Pseudomonas aeruginosa" above.)

**Severe infection** — Limb-threatening diabetic foot infections and those that are associated with systemic toxicity should be treated with broad-spectrum parenteral antibiotic therapy. In most cases, surgical debridement is also necessary. Empiric therapy should include activity against streptococci, MRSA, aerobic gram-negative bacilli, and anaerobes. Appropriate regimens are outlined in the table (table 3) [47].

**Targeted therapy** — If appropriate wound cultures were submitted, antimicrobial therapy should be tailored to culture and susceptibility results when available. However, it is not always necessary to cover all microorganisms isolated from cultures [2,27]. Virulent species such as S. aureus and streptococci (group A or B) should always be covered, but in polymicrobial infections, less virulent organisms (such as coagulase negative staphylococci and enterococci) may be less important. Furthermore, if isolates are resistant to an empiric regimen to which the patient is clearly responding well, broadening the spectrum to include those isolates may not be necessary. On the other hand, if the patient is not responding, expanding therapy to target all isolated organisms may be warranted.

For those patients who were initiated on parenteral therapy, a switch to an oral regimen is reasonable following clinical improvement.

**Duration of therapy** — The duration of antibiotic therapy should be tailored to individual clinical circumstances. Patients with mild infection should receive oral antibiotic therapy in conjunction with attentive wound care until there is evidence that the infection has resolved (usually about one to two weeks). Antibiotics need not be administered for the entire duration that the wound remains open [2,27].

Patients with infection also requiring surgical debridement should receive intravenous antibiotic therapy perioperatively. In the absence of osteomyelitis, antibiotic therapy should be administered in conjunction with attentive wound care until signs of infection appear to have resolved (two to four weeks of therapy is usually sufficient). If there is a good response to parenteral therapy, oral agents can be used to complete the course of treatment [48].

Patients requiring amputation of the involved limb should receive intravenous antibiotic therapy perioperatively. If the entire area of infection is fully resected, a brief course of oral antibiotic therapy (about a week) following surgery is usually sufficient [48].

**Osteomyelitis** — Similar to other types of diabetic foot infections, no data support the superiority of specific antimicrobial agents for osteomyelitis [46]. Appropriate regimens for empiric therapy are similar to that for moderate to severe diabetic foot infections (table 3).

Targeted antimicrobial therapy should be tailored to culture and sensitivity results, ideally from bone biopsy. In one retrospective study of diabetic patients with osteomyelitis of the toe or metatarsal head, remission (absence of signs of infection and no need for surgery after one year) was more likely in the 22 patients treated with regimens guided by bone biopsy data compared with the 28 treated based on swab culture data (82 versus 50 percent) [49]. Of note, those who had bone culture were also more likely to be treated with a rifampicin-containing regimen, which likely was a confounding variable and limits the interpretation of this finding.

For those patients who were initiated on parenteral therapy, a switch to an oral regimen is reasonable following clinical improvement. Antibiotic therapy for osteomyelitis is discussed in detail elsewhere. (See "Overview of osteomyelitis in adults", section on ‘Antibiotic selection’.)

Many patients with osteomyelitis of the foot benefit from surgical resection. In a systematic review of studies evaluating treatment of diabetic foot osteomyelitis, there was no study that directly compared surgical intervention to nonsurgical management [50]. However, studies of prolonged antibiotic therapy without resection reported success rates comparable to those reported with surgery, about 60 to 90 percent. Furthermore, partial amputations of the foot (eg, ray or transmetatarsal amputations) may adversely alter the biomechanics of the foot, increasing the risk of future ulceration. Thus, in certain cases, limited surgical debridement combined with prolonged antibiotic therapy may be appropriate [2,27]. However, extensive surgical debridement or resection is preferable in the following clinical circumstances [2]:

- Persistent sepsis without an alternate source
- Inability to receive or tolerate appropriate antibiotic therapy
- Progressive bone deterioration despite appropriate antibiotic therapy
- Mechanics of the foot are compromised by extensive bony destruction requiring correction
- Surgery is needed to achieve soft tissue wound or primary closure

The duration of antibiotic therapy of osteomyelitis depends on the extent of residual affected tissue. If all infected and necrotic bone and soft tissue has been resected (eg, amputation), then a brief course (ie, about a week) of antibiotics is likely adequate. Otherwise, the optimal duration is uncertain. Four to six weeks is an appropriate course if there is residual
infected bone following debridement of necrotic bone. However, if necrotic bone remains, clinical cure may require several months of antibiotic therapy. (See "Overview of osteomyelitis in adults", section on 'Duration of therapy'.)

Adjuvant therapies — Adjunctive therapies for treatment of diabetic foot infections include vacuum-assisted wound closure, hyperbaric oxygen and granulocyte colony-stimulating factor (G-CSF) [51-53].

Of these, vacuum-assisted wound closure is used most frequently. In a randomized trial evaluating vacuum-assisted wound closure including 342 patients with diabetic foot ulcers, complete ulcer closure was achieved more often among those who used vacuum-assisted closure than those who did not (43 versus 29 percent, respectively) [51]. Vacuum-assisted closure and hyperbaric oxygen therapy are discussed in detail separately. (See "Management of diabetic foot lesions" and "Hyperbaric oxygen therapy", section on 'Infection' and "Hyperbaric oxygen therapy", section on 'Nonhealing ulcers, skin grafts, and wound healing'.)

The role of G-CSF in managing diabetic foot infections is not clear. In a meta-analysis of five trials that included 167 patients, there was a reduction in the rates of surgical intervention and amputation, specifically, associated with the use of G-CSF (relative risks 0.38 [95% CI 0.21 to 0.70] and 0.41 [95% CI 0.18 to 0.95], respectively, compared with no G-CSF) and no significant difference in adverse effects [54]. There was no clear benefit to G-CSF with regards to infection resolution or improvement. The included studies were all of small size, and there was substantial clinical heterogeneity across studies, including variable antibiotic regimens used, G-CSF formulations and doses, and severity of underlying infection. Additional data are needed before G-CSF can be recommended or its high cost can be justified for use in diabetic foot infections.

Follow-up — Close follow-up is important to ensure continued improvement and to evaluate the need for modification of antimicrobial therapy, further imaging, or additional surgical intervention. Wound healing and a decrease in previously elevated inflammatory markers can be signs of clinical resolution, and may be particularly helpful in cases of osteomyelitis. If clinical evidence of infection persists beyond the expected duration, issues of patient adherence to therapy, development of antibiotic resistance, an undiagnosed deeper infection (eg, abscess or osteomyelitis), or ischemia should be evaluated [4].

If infection in a clinically stable patient fails to respond to more than one antibiotic course, some favor discontinuing antimicrobial therapy to optimize the yield of culture specimens obtained a few days later [4]. In general, this is a safe and reasonable approach, although deep cultures are often positive even if therapy is continued up to the time of debridement.

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient information: Diabetes and infections (The Basics)")

SUMMARY AND RECOMMENDATIONS

- Hyperglycemia, sensory and autonomic neuropathy, and peripheral arterial disease all contribute to the pathogenesis of lower extremity infections in diabetic patients. These infections are associated with substantial morbidity and mortality. (See 'Introduction' above.)
- Evaluation of a patient with a diabetic foot infection involves determining the extent and severity of infection through clinical and radiographic assessment, identifying and addressing underlying factors that predispose to and promote infection, assessing the microbial etiology, and determining the need for surgical intervention. (See 'Overview of approach to the patient' above.)
- Laboratory testing should include blood work to evaluate for leukocytosis as well as blood glucose, electrolytes, and renal function values so that glycemic control and acid base status can be evaluated and monitored. Baseline and subsequent inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) can be useful for monitoring response to therapy. Conventional radiographs should be done to evaluate for bony and soft tissue deformity or abnormalities. Formal vascular evaluation is warranted in cases where peripheral arterial insufficiency is suspected. (See 'Overview of approach to the patient' above.)
- The presence of two or more features of inflammation (erythema, warmth, tenderness, swelling, induration, or purulent secretion) can establish the diagnosis of a diabetic foot infection. The definitive diagnosis of osteomyelitis is made through histologic and microbiologic evaluation of a bone biopsy sample. However, certain clinical factors can support the presumptive diagnosis of osteomyelitis in the absence of biopsy:
  - Grossly visible bone or ability to probe to bone
  - Ulcer size larger than 2 cm²
Ulcer duration longer than one to two weeks

Erythrocyte sedimentation rate (ESR) >70 mm/h

Those with one or more of the above factors whose radiographs are normal or indeterminate for osteomyelitis should undergo magnetic resonance imaging (MRI). (See ‘Diagnosis’ above.)

Management of diabetic foot infections requires attentive wound management, good nutrition, antimicrobial therapy, glycemic control, and fluid and electrolyte balance. Wound management includes attentive local wound care including debridement of callus and necrotic tissue, wound cleansing, and relief of pressure on the ulcer. Consultation with a surgeon with experience in diabetic foot infection is important for cases of severe infections and most cases of moderate infections. Prompt surgical debridement is critical for cure of infections complicated by abscess, extensive bone or joint involvement, crepitus, necrosis, gangrene or necrotizing fasciitis and is important for source control in patients with severe sepsis. (See ‘Wound management’ above and ‘Surgery’ above.)

The microbiology of diabetic foot wounds varies with the severity and extent of involvement (Table 1). Superficial infections are likely due to aerobic gram-positive cocci whereas deep, chronically infected, and/or previously treated ulcers are more likely to be polymicrobial. Anaerobic organisms may also be involved in wounds with extensive local inflammation, necrosis, or gangrene. When there is concern for multidrug-resistant organisms or in cases of moderate or severe infection (including deep infections and osteomyelitis), aerobic and anaerobic cultures of deep tissue or bone biopsies should be obtained at the time of debridement. Organisms cultured from superficial swabs are not reliable for predicting the pathogens responsible for deeper infection. (See ‘Microbiology’ above and ‘Obtaining samples for culture’ above.)

Empic antibiotic therapy should be selected based upon the severity of infection and the likelihood of involvement of resistant organisms:

- For patients with mild infections, we suggest an empiric antimicrobial regimen (Table 2) with activity against skin flora including streptococci and Staphylococcus aureus (including methicillin-resistant Staphylococcus aureus [MRSA] if risk factors are present) (Grade 2C). (See ‘Mild infection’ above.)
- For patients with deep ulcers, we suggest an empiric antimicrobial regimen with activity against streptococci, staphylococci (and MRSA if risk factors are present), aerobic gram-negative bacilli and anaerobes (Grade 2C). Oral antibiotics (Table 2) may be appropriate for ulcers that extend to the fascia, whereas parenteral regimens (Table 3) should be used for deeper infections. (See ‘Moderate infection’ above.)
- For patients with limb-threatening diabetic foot infections or evidence of systemic toxicity, we suggest treatment with a broad-spectrum parenteral antibiotic regimen (Table 3) with activity against streptococci, MRSA, aerobic gram-negative bacilli, and anaerobes (Grade 2C). (See ‘Severe infection’ above.)

Antimicrobial therapy should be tailored to culture and susceptibility results when available, and a switch to an oral from parenteral regimen is reasonable following clinical improvement. Antibiotics need not be administered for the entire duration that the wound remains open. Close follow-up is important to ensure continued improvement and to evaluate the need for modification of antimicrobial therapy, further imaging, or additional surgical intervention. (See ‘Targeted therapy’ above and ‘Duration of therapy’ above and ‘Follow-up’ above.)

Many patients with osteomyelitis of the foot benefit from surgical resection. However, in certain cases, limited surgical debridement combined with prolonged antibiotic therapy may be appropriate. The duration of antibiotic therapy of osteomyelitis depends on the extent of residual affected tissue. (See ‘Osteomyelitis’ above.)

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REFERENCES

ic foot infections


Staphylococcal toxic shock syndrome

INTRODUCTION — *Staphylococcus aureus* causes a wide range of infections, from folliculitis and skin abscesses to bacteremia and endocarditis. *S. aureus* colonizes the skin and mucous membranes of 30 to 50 percent of healthy adults and children, most commonly in the anterior nares, skin, vagina, and rectum [1]. The organism is capable of multiplying in tissues and producing several enzymes that induce inflammation and abscesses. Many strains produce exotoxins that lead to three associated syndromes:

- Food poisoning, caused by ingestion of *S. aureus* enterotoxin
- Scalded skin syndrome, caused by exfoliative toxin
- Toxic shock syndrome (TSS), caused by toxic shock syndrome toxin-1 (TSST-1) and other enterotoxins [2-4]

Toxic shock syndrome was initially described in 1978 [5]; the disease came to public attention in 1980 with the occurrence of a series of menstrual-associated cases [6]. The majority of clinically reported cases of TSS have been due to methicillin-susceptible *S. aureus* (MSSA). Cases of TSS due to methicillin-resistant *S. aureus* (MRSA) have also emerged as rates of infection due to MRSA have increased [7,8].

The epidemiology, pathogenesis, clinical manifestations, diagnosis, and treatment of staphylococcal TSS will be reviewed here. Other issues related to staphylococcal infection are discussed separately. (See related topics.)

EPIDEMIOLOGY — Toxic shock syndrome (TSS) associated with *S. aureus* was first described in a series of pediatric cases in 1978 [5]. In 1980, the incidence rose sharply; 812 documented cases of menstruation-related TSS occurred, largely among young Caucasian women [9]. Clinical illness arose during menstruation and was associated with the use of absorbent tampons [2,10]. The incidence of TSS declined sharply after the withdrawal of some tampon brands.

Subsequently, between 2000 and 2003, the incidence rose slightly; in one report, the incidence increased from 0.8 to 3.4 per 100,000 [11]. These cases occurred among women of menstrual age but included both menstrual and nonmenstrual cases. They may have represented increased recognition due to active laboratory testing for toxin-producing strains rather than an overall increase in incidence. A study conducted in the Minneapolis area from 2000 to 2006 noted a stable incidence of staphylococcal TSS overall, with a decreasing annual incidence of menstrual TSS among women >24 years [12].

Menstrual cases — Approximately 5300 cases of TSS were reported between 1979 and 1996; underreporting is probable, especially in nonmenstrual cases [13]. The proportion of cases associated with menstruation has decreased significantly over time (91 percent between 1979 and 1980 versus 59 percent between 1987 and 1996).

The number of cases of menstrual TSS has declined, from 9 in 100,000 women in 1980 to 1 in 100,000 women since 1986 [14]. The case-fatality rate for menstrual TSS has also declined (from 5.5 percent between 1979 and 1980 to 1.8 percent between 1987 and 1996) [13].

The withdrawal of highly absorbent tampons and polyacrylate rayon-containing products from the market partially explains the decrease in menstrual cases; however, tampon use remains a risk factor for TSS [15]. Women who develop TSS are more likely to have used tampons with high absorbency, used tampons continuously for more days of their cycle, and kept a single tampon in place for longer periods of time [16].

Nonmenstrual — Approximately half of reported TSS cases are not related to menstruation [14,17]. Nonmenstrual TSS has been observed in a variety of clinical situations, including surgical and postpartum wound infections, mastitis, sepsis, sinusitis, osteomyelitis, arthritis, burns, cutaneous and subcutaneous lesions (especially of the extremities, perianal area, and axillae), respiratory infections following influenza, and enterocolitis [18-26]. Between 1979 and 1996, the proportion of cases following surgical procedures increased from 14 percent to 27 percent [13].

In one report including cases of TSS between 1979 and 1996, 93 percent occurred among women and 73 percent of nonmenstrual cases occurred among women [13]. However, one study including 130 cases noted that the gender distribution was equal with exclusion of vaginal and postpartum-associated cases [27]. Patients with nonmenstrual TSS are older (mean age 27 versus 23 years) and more often nonwhite than patients with menstrual TSS [17,23,27]. The case-fatality rate for nonmenstrual TSS was 5 percent in one report [13]. In another study of 61 TSS cases occurring in Minnesota between 2002 and 2006, there were 28 nonmenstrual cases; of these, no primary source was identified in 36 percent of cases [12].
TSS also occurs in children; between 1979 and 1996, 50 cases among children <5 years of age were reported [13]. Children <2 years accounted for approximately half of these cases, and 62 percent had antecedent cutaneous lesions.

Methicillin-resistant *S. aureus* — Methicillin-resistant *S. aureus* (MRSA) strains are capable of producing toxic shock syndrome toxin-1 (TSST-1), and patients infected with these strains may develop TSS. In a series including 30 patients with TSST-1–positive MRSA infections from France and Switzerland, five had TSS, nine had possible TSS (fever and rash without shock), two had neonatal toxic shock syndrome—like exanthematous disease (NTED), one had septic fever, and the remaining had other infections [7]. Approximately 30 percent were community acquired. NTED has also been reported in neonates in Japan and France who are colonized with TSST-1–producing MRSA [28,29].

Some data suggest that community-acquired MRSA strains may be more likely to cause TSS. In one study comparing toxin production among 85 strains (32 community-acquired MRSA strains, 32 hospital-acquired MRSA strains, and 21 *S. aureus* isolates from patients with nonmenstrual toxic shock), most community-associated MRSA strains were highly related based on molecular typing and produced either enterotoxin B (15 percent) or enterotoxin C (81 percent) but not TSST-1 [8]. The hospital-acquired strains were not related to the community-acquired strains and did not produce enterotoxin B, enterotoxin C, or TSST-1. Some correlation was observed between nonmenstrual and community-acquired strains (29 percent of nonmenstrual toxic shock strains were identical or highly related to the community-acquired strains; 16 produced either enterotoxin B or C, and none produced TSST-1).

**PATHOGENESIS** — Toxin production is an important pathogenic mechanism, as evidenced by clinical manifestations of shock, erythroderma, and multiorgan system involvement.

**Toxic shock syndrome toxin-1** — Toxic shock syndrome toxin-1 (TSST-1) was the initial exotoxin isolated from *S. aureus* isolates implicated in toxic shock syndrome (TSS) [30,31]. It is produced by 90 to 100 percent of *S. aureus* strains associated with menstrual cases of TSS and by 40 to 60 percent of strains associated with nonmenstrual cases. In studies examining the neurologic manifestations caused by TSST-1 during TSS, TSST-1 increased intracerebral prostaglandin E2 and caused caspase-dependent neuronal death in a neural cell line and in primary cortical neuron cultures in vitro [32].

The reasons that more strains causing menstrual TSS produce TSST-1 is not known. Hypotheses include structural differences that allow TSST-1 to transverse the vaginal mucosa or phenotypic differences in TSST-1 containing *S. aureus* strains that facilitate vaginal colonization [33].

Other toxins — The observation that nonmenstrual strains were less likely to produce TSST-1 led investigators to postulate the existence of other causative toxins. Staphylococcal enterotoxin B is produced by 38 to 62 percent of nonmenstrual TSST-1–negative strains, potentially implicating this toxin in TSS [34,35].

Several animal studies suggest that enterotoxin A may be a cofactor of TSST-1 [36,37]. A mutant strain deficient in enterotoxin A (but producing TSST-1) was significantly less lethal in a mouse model compared with a *S. aureus* strain that produced both toxins (70 versus 90 percent) [36]. However, TSST-1 appeared to be the principal agent of menstrual TSS in a rabbit tampon model in which strains mutant in TSST-1 (but not enterotoxin A production) were less virulent [37].

Other enterotoxins, specifically enterotoxins C, D, E, and H have been implicated in a smaller number of cases. In a study of 183 isolates of *S. aureus* from clinical specimens but not necessarily cases of TSS, 40 percent of the strains produced one or more toxins [38]. Fourteen percent of isolates produced TSST-1 and 20, 8, 6, and 3 percent, enterotoxins A, B, C, and D, respectively. Blood culture isolates were more likely to produce enterotoxin D.

Some investigators have postulated that other toxins may be more virulent than TSST-1; in one study of 32 *S. aureus* isolates from nonmenstrual TSS, 50 percent of individuals infected with a TSST-1–negative strain died, compared with 10 percent of TSST-1–positive strains [39].

**Superantigens** — *S. aureus* exotoxins cause disease because they are superantigens, which are able to activate large numbers of T cells at one time, resulting in massive cytokine production [40]. In typical T cell recognition, an antigen is taken up by an antigen-presenting cell, processed, expressed on the cell surface in complex with class II major histocompatibility complex (MHC) in a groove formed by the alpha and beta chains of class II MHC, and recognized by an antigen-specific T cell receptor. In contrast, superantigens do not require processing by antigen-presenting cells but instead interact directly with the invariant region of the class II MHC molecule. Two regions of the TSST-1 toxin within the beta 1/beta 2 and beta 3/beta 4 loops have been found to be important for MHC class II binding [41]. The superantigen-MHC complex then interacts with the T cell receptor at the variable (V) part of the beta chain. Thus, all T cells with a recognized V beta region are stimulated [42]. (See "Major histocompatibility complex (MHC) structure and function".)

Activated T cells then release interleukin (IL)-1, IL-2, tumor necrosis factor (TNF)-alpha and TNF-beta, and interferon (IFN)-gamma in large amounts, resulting in the signs and symptoms of TSS. IL-1 is an endogenous pyrogen and thus causes the high fevers associated with TSS. In addition, IL-1 mediates skeletal muscle proteolysis and probably accounts for the myalgia and elevated creatine phosphokinase (CPK) seen in TSS [43]. (See "Pathophysiology and treatment of fever in adults" and "Fever in infants and children: Pathophysiology and management," section on "Pathogenesis").

The production of TNF inhibits both random and chemotactic migratory polymorphonuclear leukocyte (PMN) functions. TSST-1 producing *S. aureus* do not engender a purulent response, which in part may be explained by PMN inhibition [40].
In addition, data suggest that TSST-1 and enterotoxin B repress the production of other S. aureus exoproteins, which may explain the absence of purulence in S. aureus infections associated with TSS [44]. It has also been postulated that endogenous endotoxin, most likely from the gastrointestinal tract, enhances susceptibility to TSST-1 [45].

**Antibody responses** — Host antibody responses to the S. aureus exotoxins play an important role in the pathogenesis of TSS. Approximately 70 to 80 percent of individuals develop antibody to TSST-1 by the late teenage years, and by the fourth decade 90 to 95 percent have such antibody [46,47]. One study found that 76 percent of infants from birth to six months of age had positive antibody titers to TSST-1, compared with only 30 to 33 percent of infants between the ages of seven months and two years. Thus, the age of six months to two years corresponds with a period of vulnerability as passive immunity is waning and acquired antibodies have not been obtained [48].

Patients with clinical TSS lack antibody to TSST-1 and often fail to develop appropriate antibodies in convalescent serum [49]. Decreased titers to the other staphylococcal enterotoxins in patients with TSS have been reported [30]. Individuals with TSS may fail to have an appropriate antibody response because superantigen-mediated production of IFN-gamma inhibits polyclonal immunoglobulin production [50]. This failure to develop antibodies may explain why some patients are predisposed to relapse after a first episode of TSS.

It is likely that varying factors are responsible for how superantigen-mediated disease affects different hosts. Genetically determined tendencies to produce different amounts of cytokines as well as titer of circulating antitoxin antibodies and the particular V beta segment that is recognized all probably play a role.

**CLINICAL MANIFESTATIONS** — The Centers for Disease Control and Prevention (CDC) established clinical criteria for toxic shock syndrome (TSS) in 1981 (table 1). These criteria were established for epidemiologic surveillance and should be not be used to exclude a case that is highly suspicious for TSS, even if all criteria are not met.

Clinical manifestations of toxic shock syndrome include fever, hypotension, and skin manifestations [3,4]. Additional symptoms and signs include chills, malaise, headache, sore throat, myalgias, fatigue, vomiting, diarrhea, abdominal pain, and orthostatic dizziness or syncope.

The symptoms and signs of TSS develop rapidly, usually in otherwise healthy individuals. The median interval between the onset of menstruation and TSS in menstrual cases is two to three days [51]; and the onset of symptoms in postsurgical cases is two days, although the onset has been reported as late as 65 days postoperatively [18,27].

During the initial 48 hours of hospitalization, patients may develop diffuse erythroderma, severe watery diarrhea, decreased urine output, cyanosis, and edema of the extremities. Neurologic symptoms such as somnolence, confusion, irritability, agitation, and hallucinations may occur secondary to cerebral ischemia and edema.

**Hypotension** — The rapid onset of hypotension, defined as either a systolic blood pressure of ≤90 mmHg for adults or less than fifth percentile by age for children <16 years of age, or an orthostatic decline in diastolic blood pressure of ≥15 mmHg, or orthostatic syncope or dizziness, often leads to subsequent tissue ischemia and organ failure. Hypotension is caused by a decrease in systemic vascular resistance as well as nonhydrostatic leakage of fluid from the intravascular space to the interstitial space [52], both of which occur as a consequence of the massive cytokine release induced by the responsible toxins. The hypotension can be unresponsive to large amounts of intravenous fluids and can persist for several days.

**Skin manifestations** — A variety of skin manifestations are seen in TSS. The initial erythroderma involves both the skin and the mucous membranes and is characterized by a diffuse, red, macular rash resembling sunburn that also involves the palms and soles (picture 1 and picture 2). This rash can be subtle and fleeting. In postoperative TSS, the erythema may be more intense around the involved surgical wound site. Mucosal involvement includes conjunctival-scleral hemorrhage and hyperemia of the vaginal and oropharyngeal mucosa (picture 3) [53]. In more severe cases, superficial ulcerations occur on the mucous membranes, and petechiae, vesicles, and bullae develop. Patients also have nonpitting edema due to increases in interstitial fluid.

Late-onset skin manifestations include a pruritic maculopapular rash that may occur one to two weeks after the disease onset and desquamation of the palms and soles that characteristically begins one to three weeks after illness develops (picture 4). Since desquamation occurs late, this is not used for acute diagnosis of TSS. In some cases, TSS may not be considered in the differential diagnosis until later when desquamation is observed; this is particularly true in nonmenstrual disease [54]. Some patients also experience loss of hair and nails one to two months following onset of illness, with regrowth by six months.

**Multiorgan system involvement** — TSS can involve all organ systems. Many patients report diffuse myalgias and weakness as presenting symptoms, which are usually accompanied by an increase in serum concentrations of creatine phosphokinase (CPK). Gastrointestinal symptoms are also common, particularly profuse diarrhea. Both pererenal and intrinsic renal failure can occur and are often accompanied by other metabolic abnormalities including hyponatremia, hypoproteinemia, hypocalemia, and hypophosphatemia [55].

Encephalopathy, manifested by disorientation, confusion, or seizure activity, can be a presenting symptom of TSS [56] and is probably due to cerebral edema [57]. Other central nervous system (CNS) findings have been reported in some patients. Persistent neuropsychological sequelae can develop such as headaches, memory loss, and poor concentration [58]. Other
findings include pulmonary edema and pleural effusions, depression of myocardial function [59], hepatic dysfunction, and hematologic abnormalities, such as anemia and thrombocytopenia.

**Menstrual versus nonmenstrual cases** — The clinical presentations of menstrual and nonmenstrual TSS are similar. In one small study, nonmenstrual TSS was associated with earlier onset of rash and fever, more pronounced renal and CNS complications, and less musculoskeletal involvement [60]. Surgical wound sites and cutaneous infections that harbor toxin-producing *S. aureus* are frequently benign, appearing without obvious purulence [27,60].

**Recurrent illness** — Episodes of recurrent TSS have been reported. Recurrent TSS tends to occur in patients who have not been treated with appropriate courses of antistaphylococcal antimicrobials and who fail to develop an appropriate antibody response to staphylococcal toxins [23,54,61]. In menstrual TSS, recurrent episodes are generally milder than the initial disease [61].

Recurrence can occur days to months after the initial episode. There is also a variant of TSS described in patients with the acquired immunodeficiency syndrome (AIDS); this presentation is characterized by a subacute illness with persistent and recalcitrant erythoderma, desquamation, mucosal injection, fever, and hypotension lasting or recurring over a period of weeks [62].

**Laboratory findings** — Abnormalities in clinical laboratory tests reflect shock and organ failure. Leukocytosis may not be present, but the total number of mature and immature neutrophils usually exceeds 90 percent, with immature neutrophils accounting for 25 to 50 percent of the total number of neutrophils. Thrombocytopenia and anemia are present during the first few days, frequently accompanied by prolonged prothrombin and partial thromboplastin times. Disseminated intravascular coagulation may be present.

Other laboratory abnormalities reflect multiorgan failure with elevated blood urea nitrogen and creatinine, elevated liver function tests, and an elevated creatine phosphokinase [55,63,64]. Most laboratory tests will return to normal 7 to 10 days after disease onset.

**DIAGNOSIS** — The diagnosis of toxic shock syndrome (TSS) is based upon clinical presentation (table 1) [4,65]. To meet the Centers for Disease Control and Prevention (CDC) case definition for a confirmed case, patients must have fever >38.9°C, hypotension, diffuse erythoderma, desquamation (unless the patient dies before desquamation can occur), and involvement of at least three organ systems. A patient who is missing one of the characteristics of the confirmed case definition may be considered a probable case. However, the CDC criteria were established for epidemiologic surveillance and should be not be used to exclude a case that is highly suspicious for TSS, even if all criteria are not met.

The isolation of *S. aureus* is not required for the diagnosis of staphylococcal TSS. *S. aureus* is recovered from wound or mucosal sites in 80 to 90 percent of patients with TSS [61] and recovered from blood cultures in approximately 5 percent of cases [27]. (See “Epidemiology, clinical manifestations, and diagnosis of streptococcal toxic shock syndrome”.)

Cultures from mucosal and wound sites should be obtained because *S. aureus* isolates can be tested for toxin production in research laboratories. In addition, acute and convalescent serum can be analyzed for antibody responses to various *S. aureus* exotoxins. The presence of a strain of *S. aureus* that produces toxin in a patient who does not have acute phase antibody to the toxin is highly suggestive of TSS. These tests can be helpful in making a retrospective diagnosis in cases suspicious for TSS.

**DIFFERENTIAL DIAGNOSIS** — Few illnesses lead to the rapid onset of shock symptoms in young, healthy people, as in the case of staphylococcal toxic shock syndrome (TSS). Other diagnostic considerations include streptococcal TSS, which is most often associated with severe pain and tenderness signifying infection at a site of local trauma, in addition to the other manifestations of TSS. It is important to distinguish between these two entities because patients with streptococcal TSS may require immediate surgical debridement of the involved site. (See "Treatment of streptococcal toxic shock syndrome").

Other diagnostic possibilities include Rocky Mountain spotted fever (RMSF), although the rash associated with RMSF typically is petechial, involves the extremities first, and occurs an average of three days after the development of fever. (See "Clinical manifestations and diagnosis of Rocky Mountain spotted fever").

Meningococcemia is another important diagnostic consideration for shock in a young person; again, the petechiae and purpura found in this disease are different from the skin findings in *S. aureus* TSS. In addition, meningitis is frequently seen in conjunction with meningococcemia and is rare in TSS. (See "Clinical manifestations of meningococcal infection").

Other more unusual illnesses can be considered if there is an appropriate exposure such as leptospirosis, dengue hemorrhagic fever, and typhoid fever. (See “Epidemiology, microbiology, clinical manifestations, and diagnosis of leptospirosis” and “Clinical manifestations and diagnosis of dengue virus infection” and “Epidemiology, microbiology, clinical manifestations, and diagnosis of typhoid fever”.)

In addition to the aforementioned illnesses, the differential diagnosis for patients with suspected TSS should include nosocomially acquired sepsis from gram-negative or gram-positive pathogens. These organisms should be recovered in blood cultures to make a diagnosis; the type of bacterium isolated may provide a clue about the origin of the infection.
MANAGEMENT

Clinical evaluation — The mainstay of treatment for toxic shock syndrome (TSS) is supportive while hypotension is present. An examination for the presence of foreign material in the vaginal canal (eg, tampons, contraceptive sponges) should be undertaken, and these materials should be removed. Culture of the vaginal canal in cases of menstrual TSS (and, in nonmenstrual cases, of material obtained from an infectious focus) should be submitted for culture and susceptibility testing.

Supportive therapy — Patients may require extensive fluid replacement (10 to 20 liters per day) to maintain perfusion because of intractable hypotension and diffuse capillary leak. Although the blood pressure may improve with fluids alone, vasopressors (eg, dopamine and/or norepinephrine) may also be required. (See "Evaluation and management of severe sepsis and septic shock in adults," and "Systemic inflammatory response syndrome (SIRS) and sepsis in children: Definitions, epidemiology, clinical manifestations, and diagnosis" and "Use of vasopressors and inotropes".)

Menstrual TSS can resolve with supportive care alone, although recurrences were noted in the early case series in which antistaphylococcal antibiotics were not administered [61].

Surgical therapy — Drainage of any identified infectious focus is essential. In postsurgical patients, surgical wounds may not appear to be infected because of decreased inflammatory response but should be explored nevertheless and debrided if warranted.

Antibiotic therapy — Antistaphylococcal antibiotic therapy is needed to eradicate organisms and to prevent recurrences [6,61]. We recommend that:

● All patients with suspected TSS receive empiric treatment with **clindamycin** (adults: 900 mg intravenously [IV] every eight hours; children: 25 to 40 mg/kg per day in three divided doses) **plus vancomycin** (adults: 15 to 20 mg/kg/dose every 8 to 12 hours, not to exceed 2 g per dose; children: 40 mg/kg per day IV in four divided doses).

If culture and sensitivity results are available, we recommend that:

● Patients with TSS due to methicillin-susceptible **S. aureus** (MSSA) receive **clindamycin** (if susceptible) (adults: 900 mg IV every eight hours; children: 25 to 40 mg/kg per day in three divided doses) **plus oxacillin** or **nafcillin** (2 g IV every four hours; children: 100 to 150 mg/kg per 24 hours IV in four divided doses).

● Patients with TSS due to methicillin-resistant **S. aureus** (MRSA) receive **clindamycin** (if susceptible) (adults: 900 mg IV every eight hours; children: 25 to 40 mg/kg per day in three divided doses) **plus vancomycin** (adults: 15 to 20 mg/kg/dose every 8 to 12 hours, not to exceed 2 g per dose; children: 40 mg/kg per day IV in four divided doses) or **linezolid** alone (adults: 600 mg oral or IV every 12 hours; children: 10 mg/kg IV oral or IV every 12 hours) or in combination with vancomycin, depending on the source of infection.

While **clindamycin** may be adequate single-drug therapy for a drained infected focus such as a surgical wound, we recommend combination therapy of clindamycin and an antistaphylococcal penicillin (eg, **oxacillin** or **nafcillin** or **vancomycin** for patients with deep-seated infections (eg, osteomyelitis) or bacteremia, at least until hemodynamics have stabilized. **Linezolid** can be considered as a second agent for deep-seated infections in the event of resistance to clindamycin. Antibiotic therapy clearly reduces the likelihood of recurrent TSS by eliminating the carrier state [61].

Theoretically, antibiotics such as **clindamycin** that suppress protein synthesis and, therefore, toxin synthesis may be more efficacious than cell wall–active agents such as beta-lactams. This finding has been demonstrated in vitro; subinhibitory concentrations of clindamycin, **erythromycin**, **rifampin**, and **fluoroquinolones** suppressed toxic shock syndrome toxin-1 (TSST-1) synthesis by 90 percent, while five different beta-lactam antibiotics, including **nafcillin** and **cephalosporins**, increased measurable TSST-1 in culture supernatants, probably by lysis or increasing cell membrane permeability [56].

A case report of successful treatment of TSS with **linezolid** and in vitro analysis of TSST-1 synthesis of the S. aureus isolate supports the superior efficacy of protein synthesis inhibitors (clindamycin and linezolid) to cell wall–active agents (vancomycin and beta-lactam antibiotics) in TSS [67]. The patient's S. aureus isolate was cultured in medium to optimize TSST-1 production in the presence or absence of antibiotics. Maximal TSST-1 production occurred in the untreated, nafcillin-treated, and vancomycin-treated cultures. In contrast, linezolid and clindamycin completely suppressed toxin synthesis.

No randomized controlled studies have evaluated antibiotic regimens for treatment of TSS, thus recommendations are based upon animal studies and clinical case series.

Duration of therapy — We typically treat with a one to two week course of an antistaphylococcal agent, even in the absence of overt S. aureus infection.

Eradication of carrier state — In patients with S. aureus TSS, nares cultures should be obtained; if nasal carriage is present, an attempt should be made to eradicate it with **mupirocin**. Treatment with mupirocin involves applying one-half of the ointment from a single-use tube into one nostril and the other half into the other nostril twice daily for five days.

However, there are no data to support this practice. In one study examining the effect of topical antimicrobials on TSST-1 production, **silver** sulphadiazine, which is used routinely for burns, caused a fourfold increase in toxin production in 45
percent of strains. In contrast, mupirocin ointment decreased toxin production in 47 percent of strains and caused no increased toxin from any strains [68].

Additional therapies

Intravenous immune globulin — Use of intravenous immune globulin (IVIG) therapy in staphylococcal TSS is a logical therapy if an individual is susceptible to TSS because of diminished antibody production to toxin [69-72]. Treatment with IVIG may be efficacious in streptococcal toxic shock, another superantigen-mediated disease [73-75]. A report from Sweden noted that culture supernatants containing superantigen from S. aureus were less efficiently inhibited by IVIG than those from S. pyogenes [76]. (See “Treatment of streptococcal toxic shock syndrome”, section on ‘Intravenous immune globulin’.)

There have been no controlled trials of IVIG therapy in staphylococcal TSS. A single case report of the use of IVIG in staphylococcal TSS describes a 39-year-old man with HIV infection and diffuse erythema of the arms and legs, desquamation of the arms, hands, feet, and eyebrows, pharyngeal erythema, and a toe lesion that grew a TSST-1 producing S. aureus [62]. He was treated with IVIG (200 mg/kg per day) for five days after failing antibiotic therapy and had resolution of his symptoms.

It seems reasonable to use IVIG in cases of TSS that are recognized early in their course but have not responded to fluids and vasopressors. In a trial of streptococcal TSS, IVIG was given for three consecutive days at 1 g/kg on day one followed by 0.5 g/kg on days two and three. In this study (which was stopped early because of slow patient recruitment) patients treated with adjunctive IVIG had a non–statistically significant improvement in mortality [74]. Based on the Swedish report noted above, higher doses of IVIG may be necessary in TSS due to S. aureus [76]. (See “General principles in the use of immune globulin”.)

Corticosteroids — We do not favor corticosteroid treatment in TSS because of the limited clinical data with this therapy. Some investigators have advocated the use of high dose corticosteroids (methylprednisolone 10 to 30mg/kg per day) for TSS [77]. In a retrospective study in which 25 patients who received steroids were compared with 20 patients who did not, patients treated within two to three days of the onset of TSS had reduced severity of illness and duration of fever, although there was no difference in mortality.

PROGNOSIS — Death associated with toxic shock syndrome (TSS) usually occurs within the first few days of hospitalization but may occur as late as two weeks after admission. Fatalities have been attributed to refractory cardiac arrhythmias, cardiomyopathy, irreversible respiratory failure, and, rarely, bleeding caused by coagulation defects [78,79].

The TSS-related mortality rate in menstrual cases has decreased since the syndrome was first recognized in 1980, from 5.5 to 1.8 percent between 1987 and 1996 [13]. The mortality due to nonmenstrual TSS is higher and has remained essentially unchanged between 1980 and 1996, at approximately 6 percent [13,15]. The mortality due to TSS in children is 3 to 5 percent [80].

Patients who have had tampon-associated TSS should not resume using tampons.

SUMMARY AND RECOMMENDATIONS

● Staphylococcus aureus strains produce exotoxins that lead to three syndromes: food poisoning, caused by ingestion of S. aureus enterotoxin; scalded skin syndrome, caused by exfoliative toxin; and toxic shock syndrome (TSS), caused by toxic shock syndrome toxin-1 (TSST-1) and other enterotoxins. (See ’Introduction’ above.)

● Approximately half of reported TSS cases are menstrual, associated with highly absorbent tampons. Nonmenstrual TSS has been associated with surgical and postpartum wound infections, mastitis, sepsis, peritonitis, burns, and cutaneous and subcutaneous lesions (especially of the extremities, perianal area, and axillae), and respiratory infections following influenza. (See ’Epidemiology’ above.)

● Methicillin-resistant S. aureus (MRSA) strains can produce TSST-1, and patients infected with these strains may develop TSS. (See ’Methicillin-resistant S. aureus’ above.)

● Host antibody responses to the S. aureus exotoxins play an important role in the pathogenesis of TSS. Seventy to 80 percent of individuals develop antibody to TSST-1 by the late teenage years, and by the fourth decade 90 to 95 percent have such antibody. Patients with clinical TSS lack antibody to TSST-1 and often fail to develop appropriate antibodies in convalescent serum. (See ’Antibody responses’ above.)

● The symptoms and signs of TSS develop rapidly, usually in otherwise healthy individuals. Patients with TSS commonly have fever, hypotension, and skin manifestations. In addition, TSS can involve all organ systems (table 1). The Centers for Disease Control and Prevention (CDC) case definition criteria established for epidemiologic surveillance should not be used to exclude a case that is highly suspicious for TSS, even if all criteria are not met. (See ’Clinical manifestations’ above.)

● The CDC case definition for a confirmed case includes the following: fever >38.9°C, hypotension, diffuse erythroderma, desquamation (development of desquamation may be delayed), and involvement of at least three organ systems (table 1). A probable case is a patient who is missing one of the characteristics of the confirmed case definition. The isolation of S. aureus is not required for the diagnosis of staphylococcal TSS. (See ’Diagnosis’ above.)
The mainstay of treatment for TSS is supportive while hypotension is present. An examination for the presence of foreign material in the vaginal canal (eg, tampons, contraceptive sponges) should be undertaken, and this material should be removed. Drainage of any identified infectious focus is essential. Exploration of surgical wounds in postoperative TSS is imperative. (See ‘Management’ above.)

It is not clear whether antibiotics alter the course of acute TSS. No randomized controlled studies have evaluated antibiotic regimens for treatment of TSS; thus, recommendations are based upon animal studies and clinical case series. We recommend that all patients with suspected TSS receive combination antibiotic therapy (Grade 1C), at least until the patient stabilizes. (See ‘Antibiotic therapy’ above.)

We typically use the following regimens (see ‘Antibiotic therapy’ above):

- Empiric treatment with clindamycin (adults: 900 mg intravenously [IV] every eight hours; children: 25 to 40 mg/kg per day in three divided doses) plus vancomycin (adults: 15 to 20 mg/kg/dose every 8 to 12 hours, not to exceed 2 g per dose; children: 40 mg/kg per day IV in four divided doses).
- In patients with TSS due to methicillin-susceptible S. aureus (MSSA), we use clindamycin (if susceptible) (adults: 900 mg every eight hours; children: 25 to 40 mg/kg per day in three divided doses) plus oxacillin or nafcillin (2 g IV every 4 hours; children: 100 to 150 mg/kg per 24 hours IV in four divided doses).
- In patients with TSS due to methicillin-resistant S. aureus (MRSA), we use clindamycin (if susceptible) (adults: 900 mg IV every eight hours; children: 25 to 40 mg/kg per day in three divided doses) plus vancomycin (adults: 15 to 20 mg/kg/dose every 8 to 12 hours, not to exceed 2 g per dose; children: 40 mg/kg per day IV in four divided doses) or linezolid alone (adults: 600 mg oral or IV every 12 hours; children: 10 mg/kg oral or IV every 12 hours) or in combination with vancomycin, depending on the source of infection.

We typically treat with a one to two week course of an antistaphylococcal agent even in the absence of overt S. aureus infection. (See ‘Duration of therapy’ above.)

We suggest screening for S. aureus nasal carriage in patients with S. aureus TSS followed by treatment with mupirocin in those with positive nares cultures. (Grade 2C). (See ‘Eradication of carrier state’ above.)

We suggest treatment with intravenous immune globulin (1 g/kg in a single dose administered over several hours on day one, with a repeat dose of 0.5 mg/kg on days two and three) in severe cases of TSS in patients that are recognized early in their course who have not responded to fluids and vasopressors (Grade 2C). (See ‘Intravenous immune globulin’ above.)

We recommend NOT treating with corticosteroids in TSS. (Grade 1C). (See ‘Corticosteroids’ above.)

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INTRODUCTION — Streptococcal toxic shock syndrome (TSS) is a clinical illness characterized by shock and multiorgan failure. Streptococcal TSS consists of isolation of group A *Streptococcus* (GAS) from a normally sterile body site, together with hypotension, tachycardia, and evidence of organ failure, such as acute respiratory distress syndrome, coagulopathy, liver failure, or renal failure [1]. It occurs as a result of capillary leak and tissue damage due to release of inflammatory cytokines induced by streptococcal toxins.

Streptococcal TSS occurs most frequently in the setting of invasive infection due to group A *Streptococcus* (*Streptococcus pyogenes*). GAS typically causes pharyngitis or skin and soft tissue infection; these are generally responsive to appropriate antibiotic therapy, and patients do not develop streptococcal TSS [2]. Less commonly, GAS causes invasive disease such as necrotizing infection of the skin and fascia, gangrenous myositis, bacteremia, or pneumonia [3], and these types of infection are complicated by TSS in approximately one-third of cases [4].

The epidemiology, clinical manifestations, and diagnosis of streptococcal toxic shock syndrome will be reviewed here. The treatment of streptococcal toxic shock syndrome is discussed separately. (See "Treatment of streptococcal toxic shock syndrome").

EPIDEMIOLOGY — Invasive infections associated with group A streptococcal (GAS) toxic shock syndrome (TSS) have been reported with increasing frequency, predominantly from North America and Europe [1,4-13]. There are an estimated 3.5 cases of streptococcal TSS per 100,000 persons, with a case-fatality rate of 30 to 60 percent [3,13-16]. One study noted an increase in the incidence of invasive group A streptococcal disease in Utah between 2002 and 2010, from 3.5 to 9.8 cases per 100,000 [17]. Up to one-third of patients with invasive GAS disease developed TSS in reported case series [15,18]. The rate of TSS among patients with necrotizing fasciitis is approximately 50 percent [3,19].

All topics are updated as new evidence becomes available and our peer review process is complete. Literature review current through: Mar 2015. | This topic last updated: Dec 01, 2014.
Risk factors — GAS TSS occurs among all age groups. Most patients are not immunosuppressed; diabetes and alcoholism are risk factors described in some studies [7,20-25]. Among reports of invasive GAS infections associated with bacteremia in the late 1980s, most patients were either <10 or >60 years of age and had underlying diseases, such as cancer, renal failure, leukemia, and severe burns, or were receiving corticosteroids or other immunosuppressive drugs [20-24]. Invasive infection remains highest in patients >50 years of age.

Subsequently, the frequency of invasive disease and streptococcal TSS has increased among patients 20 to 35 years of age. This likely reflects increased frequency of two presentations of infection: (1) pregnancy-associated GAS infections and (2) deep infection at the site of muscle injury or blunt trauma, in the absence of a clear portal of entry [26-29].

The following factors have been associated with the development of severe GAS infection [4]:

- Minor trauma, including injuries resulting in hematoma, bruising, or muscle strain
- Use of nonsteroidal antiinflammatory drugs (NSAIDs)
- Recent surgery (eg, liposuction, hysterectomy, bunioectomy, bone pinning, breast reconstruction [30], cesarean section [31])
- Viral infection (eg, influenza, varicella) [32]
- Postpartum state (see "Infection associated with pregnancy" below)

Among children, varicella infection is a risk factor for invasive GAS infection and TSS [32-35]. In Germany, one study including more than 1300 cases of invasive GAS infection noted association with varicella in approximately 1.5 percent of cases; complications included sepsis (43 percent), streptococcal TSS (24 percent), and necrotizing fasciitis (19 percent) [34]. In the United States, introduction of universal varicella vaccination has been associated with a decline in the rate of varicella-associated invasive GAS infection (27 to 2 percent) between the early 1990s and the early 2000s [35].

The association between NSAIDs and severe GAS infection may be attributable to NSAID use for relief of pain associated with traumatic injury. In one retrospective study, authors postulated that NSAID use masked presenting symptoms, delaying diagnosis, or served as an independent predisposing factor to more severe streptococcal infection and shock [4]. Predisposition to GAS TSS due to NSAIDs could be mediated via inhibition of neutrophil function, suppression of fever, and augmentation of cytokine release [36].

GAS infections usually occur sporadically; they are not generally associated with clusters of cases, although outbreaks of severe GAS infections have occurred in nursing homes [37,38] and among hospitalized patients [39].

MICROBIOLOGY — Streptococcal toxic shock syndrome (TSS) occurs most frequently in the setting of infection due to group A Streptococcus (GAS; Streptococcus pyogenes). GAS is an aerobic gram-positive coccus that releases exotoxins that act as superantigens; they are capable of activating the immune system by bypassing the usual antigen-mediated immune response sequence, resulting in the release of large quantities of inflammatory cytokines. Virulence factors and other aspects of GAS pathogenesis are discussed separately. (See "Group A streptococcus: Virulence factors and pathogenic mechanisms".)

Group B, group C, and group G streptococci have also been associated with toxic shock syndrome. (See "Group B streptococcal infections in nonpregnant adults" and "Group C and group G streptococcal infection".)

Streptococcus suis has emerged as a cause of streptococcal toxic shock-like syndrome (STSLS) [40]. Although this pathogen is traditionally associated with bacterial meningitis, a highly pathogenic strain has emerged with the ability to produce massive quantities of proinflammatory cytokines. (See "Epidemiology of bacterial meningitis in adults".)

CLINICAL MANIFESTATIONS

Shock — The most common portals of entry for group A Streptococcus (GAS) are the skin, vagina, and pharynx. However, no portal of entry is identified in up 45 percent of patients who develop GAS toxic shock syndrome (TSS) [4].

Toxic shock syndrome due to GAS typically presents with pain that precedes physical findings of infection [4]. At the site of minor trauma (such as a bruise, strained muscle, or sprained ankle), patients may develop deep infection such as necrotizing fasciitis or myonecrosis within 24 to 72 hours, often with no visible break in the skin. The pain typically involves soft tissue of an extremity but may also mimic peritonitis, pelvic inflammatory disease, pneumonia, acute myocardial infarction, cholecystitis, or pericarditis [41-43].

Clinical signs of soft tissue infection typically consist of localized swelling and erythema followed by ecchymoses and sloughing of skin; progression to necrotizing fasciitis or myositis occurs in 70 to 80 percent of cases [4,19]. An influenza-like syndrome characterized by fever, chills, myalgia, nausea, vomiting, and diarrhea occurs in about 20 percent of patients [39]. A diffuse, scarlatinina-like erythema occurs in about 10 percent of cases [1].

Fever is common; hypothermia may be present in patients with shock. Altered mental status is observed in about half of patients. Patients may be normotensive on presentation but become hypotensive within the subsequent four hours in about half of cases. Shock is due to both capillary leak and vasodilatation. Despite aggressive therapy, the systolic pressure remains depressed after eight hours in 90 percent of patients [4].
A variety of clinical manifestations may be observed in patients without soft tissue findings (about 20 percent of cases). These include endophthalmitis, perihepatitis, peritonitis, infection associated with pregnancy, myocarditis, pneumonia, varicella infection, or overwhelming sepsis [42]. GAS TSS is a very rare complication of streptococcal pharyngitis in adults but may be more common in children [44].

Complications of GAS TSS include bacteremia, renal failure, acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation, and, rarely, Waterhouse-Friderichsen syndrome [45]. ARDS occurs in approximately 55 percent of cases, generally after the onset of hypotension [4].

Renal dysfunction occurs among nearly all patients within 48 to 72 hours. Hypotension, myoglobinuria and hemoglobinuria (due to toxin-induced hemolysis) can contribute to the development of acute renal failure. Many patients require dialysis for up to three weeks. In patients who survive, the serum creatinine concentration returns to baseline within four to six weeks.

Initial laboratory studies may demonstrate mild leukocytosis with significant left shift [4]. The serum creatinine concentration is frequently elevated and precedes the development of hypotension in 40 to 50 percent of cases [4]. Other common findings include hypoalbuminemia, hypocalcemia, positive blood cultures (in approximately 60 percent of cases), and an increase in the serum creatinine kinase concentration, which suggests the presence of necrotizing fasciitis or myositis [4].

Infection associated with pregnancy — GAS infection associated with pregnancy (also referred to as puerperal sepsis or postpartum infection) was first described by Semmelweis in the 1850s and remains an important cause of maternal and infant mortality worldwide [26,46]. Approximately 14 percent of GAS postpartum infections are nosocomially acquired [16]: onset of postpartum infection can also occur in the community after hospital discharge. Nearly 20 percent of cases of GAS infection occur during the third trimester, prior to onset of labor or rupture of membranes [26].

Patients with puerperal sepsis due to GAS typically present with fever, abdominal pain, and hypotension without tachycardia or leukocytosis. About 220 cases occur annually in the United States, for an overall rate of 6 cases per 100,000 live births [47]. In 2002, the case fatality rate was about 3.5 percent. Maternal mortality is highest when infection develops within four days of delivery [26] or during the late third trimester [26].

Issues related to GAS and pregnancy are discussed further separately. (See “Pregnancy-related group A streptococcal infection.”)

DIAGNOSIS — Group A streptococcal (GAS) toxic shock syndrome (TSS) must be considered in any patient presenting from the community in shock in the absence of a clear etiology. Other important findings include a history of recent trauma, severe pain, and fever. The following clinical guideline for diagnosis of GAS TSS has been established by the Working Group on Severe Streptococcal Infections [1]:

- Isolation of GAS from a normally sterile site (eg, blood; cerebrospinal, pleural, or peritoneal fluid; tissue biopsy; or surgical wound), and
- Hypotension (systolic blood pressure ≤90 mmHg in adults or <5th percentile for age in children)

Plus two or more of the following:

- Renal dysfunction (in adults, creatinine ≥2 mg/dL; in children, ≥2x the upper limit of normal for age; in patients with preexisting renal disease, ≥2x elevation over baseline)
- Coagulopathy (eg, thrombocytopenia, disseminated intravascular coagulation)
- Liver dysfunction (eg, transaminases or bilirubin ≥2x upper limit of normal; in patients with preexisting liver disease, ≥2x elevation over baseline)
- Acute respiratory distress syndrome
- Erythematous macular rash, may desquamate
- Soft tissue necrosis (eg, necrotizing fasciitis, myositis, or gangrene)

A diagnosis of probable GAS TSS can be made if GAS is isolated from a normally nonsterile site (eg, throat, vagina, skin lesion) but the patient fulfills the other criteria noted above and no other etiology for the illness is identified.

Recovery of the organism from blood cultures usually takes 8 to 24 hours. Gram stain of involved tissue demonstrating gram-positive cocci in pairs and chains can provide an early diagnostic clue in many cases.

DIFFERENTIAL DIAGNOSIS — The abrupt onset of shock in a previously healthy individual has a limited number of causes.

- Staphylococcal toxic shock syndrome (TSS) — Staphylococcal TSS should be considered in the setting of menstruating females or in association with recent surgery or localized staphylococcal abscess. The diagnosis is based on clinical presentation (Table 1). (See “Staphyloccocal toxic shock syndrome.”)
- Gram-negative sepsis — Clinical manifestations of gram-negative sepsis include fever, hypotension, and respiratory failure. In gram-negative sepsis, renal failure develops after hypotension, whereas, in group A streptococcal (GAS) TSS, renal impairment frequently precedes hypotension. The diagnosis of gram-negative sepsis is established by culture. (See “Gram-negative bacillary bacteremia in adults.”)
Typhoid fever – Clinical manifestations of typhoid include fever, relative bradycardia, or pulse-temperature dissociation and abdominal pain. In typhoid fever, the white blood count is usually normal or low; in GAS TSS, it is generally normal or elevated with a marked left shift. The diagnosis of typhoid fever is established by culture. (See "Epidemiology, microbiology, clinical manifestations, and diagnosis of typhoid fever").

Rocky Mountain spotted fever (RMSF) – Clinical manifestations of RMSF include fever, headache, and rash; in GAS TSS, headache is rare and rash is present in only 10 percent of patients. In RMSF, the rash is most often petechial, whereas, in GAS TSS, the rash is diffusely erythematous. The diagnosis of RMSF is based on clinical symptoms. (See "Clinical manifestations and diagnosis of Rocky Mountain spotted fever").

Meningococcemia – Clinical manifestations of meningococcemia include fever, nausea, vomiting, headache, and petechial rash. Symptoms of meningitis in GAS TSS are infrequent. The diagnosis of meningococcemia is established by culture. (See "Clinical manifestations of meningococcemia infection").

Streptococcus pneumoniae infection – Clinical manifestations of S. pneumoniae infection include respiratory symptoms and development of lobar consolidation and empyema; these can also occur in the setting of GAS TSS. The diagnosis of S. pneumoniae infection is established via culture. (See "Invasive pneumococcal (Streptococcus pneumoniae) infections and bacteremia").

Leptospirosis – Clinical manifestations of leptospirosis include fever, rigors, myalgia, headache, and abdominal symptoms. Conjunctival suffusion is one of the most reliable distinguishing features of leptospirosis since it rarely occurs with any other infectious illness. The diagnosis of leptospirosis is established via serologic testing. (See "Epidemiology, microbiology, clinical manifestations, and diagnosis of leptospirosis").

Heat stroke – Clinical manifestations of heat stroke include core body temperature in excess of 40°C with associated central nervous system dysfunction. Additional manifestations that may also be observed in the setting of GAS TSS include dehydration with evidence of renal impairment, hypotension, and sunburn-type erythema. The history of heat exposure is helpful in distinguishing the two illnesses. (See "Severe nonexertional hyperthermia (classic heat stroke) in adults").

SUMMARY

Streptococcal toxic shock syndrome (TSS) is a clinical illness characterized by shock and multiorgan failure; it occurs as a result of capillary leak and tissue damage due to release of inflammatory cytokines induced by streptococcal toxins. Streptococcal TSS occurs most frequently in the setting of infection due to group A Streptococcus (GAS). (See 'Introduction' above.)

There are an estimated 3.5 cases of streptococcal TSS per 100,000 persons, with a case-fatality rate of 30 to 60 percent. GAS TSS occurs among all age groups; most patients are not immunosuppressed. Risk factors associated with development of severe GAS infection include minor trauma, use of nonsteroidal antiinflammatory drugs, recent surgery, viral infection, and postpartum state. (See 'Epidemiology' above.)

Toxic shock syndrome due to GAS typically presents with pain that precedes physical findings of infection. At the site of minor trauma (such as a bruise, strained muscle, or sprained ankle), patients may develop deep infection such as necrotizing fasciitis or myonecrosis within 24 to 72 hours, often with no visible break in the skin. (See 'Epidemiology' above.)

GAS infection associated with pregnancy is an important cause of maternal and infant mortality. Patients with GAS puerperal sepsis typically present with fever, abdominal pain, and hypotension without tachycardia or leukocytosis. Maternal mortality is highest when infection develops within four days of delivery. (See 'Infection associated with pregnancy' above.)

The diagnosis of streptococcal TSS consists of hypotension and isolation of streptococci from a normally sterile site, together with two or more findings including renal dysfunction, coagulopathy liver dysfunction, acute respiratory distress syndrome, rash, and/or soft tissue necrosis. Gram stain of involved tissue demonstrating gram-positive cocci in pairs and chains can provide an early diagnostic clue in many cases. (See 'Diagnosis' above.)

The differential diagnosis of streptococcal TSS includes staphylococcal TSS, typhoid fever, Rocky Mountain spotted fever, meningococcemia, Streptococcus pneumoniae infection, leptospirosis, and heat stroke. (See 'Differential diagnosis' above.)

REFERENCES


INTRODUCTION — Streptococcal toxic shock syndrome (TSS) is a clinical illness characterized by shock and multiorgan failure; it occurs as a result of capillary leak and tissue damage due to release of inflammatory cytokines induced by streptococcal toxins.

Streptococcal TSS occurs most frequently in the setting of infection due to group A Streptococcus (GAS; Streptococcus pyogenes). GAS typically causes pharyngitis or skin and soft tissue infection; these are generally responsive to appropriate antibiotic therapy [1]. Less commonly, GAS causes invasive disease such as necrotizing infection of the skin and fascia, gangrenous myositis, bacteremia, or pneumonia [2]. Invasive disease is complicated by TSS in approximately one-third of cases [3-5].

The treatment of streptococcal toxic shock syndrome will be reviewed here. The epidemiology, clinical manifestations, and diagnosis of streptococcal toxic shock syndrome are discussed separately. (See “Epidemiology, clinical manifestations, and diagnosis of streptococcal toxic shock syndrome”.)

MANAGEMENT — Management of streptococcal toxic shock syndrome (TSS) includes treatment of septic shock and associated complications, surgical debridement of infection (if feasible), and antimicrobial therapy (table 1). Such cases frequently require coordinated care from a team, including individuals with clinical expertise in critical care, surgery, and infectious disease.

Treatment of septic shock — Streptococcal sepsis leads to diffuse capillary leak and intractable hypotension. Therefore, large quantities of intravenous (IV) fluids may be necessary to maintain perfusion (up to 10 to 20 L/day); vasopressors may also be required. The approach to management of septic shock is discussed separately. (See “Epidemic and management of severe sepsis and septic shock in adults”.)

Surgical debridement — Streptococcal TSS may occur in the setting of soft tissue infection, such as necrotizing fasciitis or myonecrosis. These entities should be suspected in patients presenting with fever and pain, followed by progression to soft tissue swelling, and formation of violaceous vesicles and bullae. Surgical exploration through a small incision with visualization of muscle and fascia and Gram stain of involved tissue may provide an early and definitive diagnosis [1].

Early aggressive surgical intervention is critical. In some settings, serial debridements are performed until tissue necrosis is no longer evident. Late debridement may be precluded by hemodynamic instability or extension of infection to areas that are difficult to debride, such as the head and neck, thorax, or abdomen. In addition, the benefit of debridement may be diminished once systemic toxicity and overt necrosis have developed. In one retrospective series including 20 patients with streptococcal TSS, major surgical procedures were warranted in more than half of cases; these included fasciotomy, surgical debridement, exploratory laparotomy, intraocular aspiration, amputation, or hysterectomy [3]. (See “Necrotizing soft tissue infections”.)

Antibiotic therapy — Empiric antimicrobial therapy should be initiated pending culture results; thereafter, antimicrobial therapy should be tailored accordingly. Regimens for empiric and tailored therapy are summarized below. (See Empiric therapy below and ‘Tailored therapy’ below.)

General principles — In general, antimicrobial treatment of streptococcal TSS consists of a beta-lactam agent (which inhibits cell wall synthesis) in combination with clindamycin (which inhibits protein synthesis).

S. pyogenes is exquisitely susceptible to beta-lactam antibiotics; however, use of penicillin monotherapy is associated with high mortality and extensive morbidity in the setting of aggressive infections associated with TSS (such as necrotizing fasciitis, empyema, burn wound sepsis, subcutaneous gangrene, and myositis) [3,6-11]. In one report including 25 cases of streptococcal myositis treated with penicillin alone, the mortality rate was 85 percent [9].

Studies of experimental infection have noted an association between penicillin and treatment failure in the presence of large numbers of organisms [12,13]. In a mouse model of myositis due to S. pyogenes, penicillin treatment was not effective when administered two hours after onset of infection [13]. In contrast, the survival rate of clindamycin-treated mice with treatment delay of 0, 2, 6, or 16.5 hours was 100, 100, 80, and 70 percent, respectively [13,14]. These observations have been attributed to inoculum size [12,15,16]. Penicillin and other beta-lactam antibiotics are believed to be most effective against rapidly growing bacteria. Thus, efficacy is likely greatest in the early stages of infection when organisms are multiplying quickly. The efficacy of beta-lactams may be diminished as higher concentrations of organisms accumulate and the rate of bacterial growth slows. In the setting of deep-seated infection, the concentration of streptococcal organisms may be sufficiently high to reduce the effectiveness of beta-lactam antibiotics [12].

It has been suggested that diminished penicillin efficacy in the setting of high inoculum may be attributable to the available numbers of penicillin-binding proteins (PBPs) on the organism surface that are available at various points during the phases of bacterial growth. In one laboratory study, fewer PBPs were observed during stationary-phase growth in vitro [15].

Thus, clindamycin is generally used in addition to beta-lactams in the treatment of invasive group A streptococcal (GAS) infection. Several observational studies have demonstrated a clinical benefit to the addition of clindamycin [5,17,18]. As an example, in a retrospective study of 84 patients with severe invasive GAS infection, use of clindamycin was associated with a lower 30-day mortality (15 versus 39 percent among those who did not receive clindamycin) [19].
**Clindamycin** has several potential advantages for treatment of GAS infection. The efficacy of clindamycin is not affected by inoculum size or stage of growth [15,19]. It suppresses synthesis of bacterial toxins [20-22], and it is associated with a longer postantibiotic effect than beta-lactam agents. In addition, clindamycin suppresses synthesis of PBPs, which are involved in cell wall synthesis and degradation (in addition to serving as binding targets for penicillin) [19].

**Antibiotic regimens** — Empiric antimicrobial therapy should be initiated pending culture results; thereafter, antimicrobial therapy should be tailored accordingly.

**Empiric therapy** — Patients presenting with clinical manifestations of streptococcal TSS should receive empiric therapy as follows, pending culture results:

- **Clindamycin** (900 mg IV every eight hours)

plus one of the following:

- A carbapenem (eg, **imipenem** 500 mg intravenously every six hours OR **meropenem** 1 g intravenously every eight hours)

- A combination drug containing a penicillin plus beta-lactamase inhibitor (eg, **ticarcillin-clavulanate** 3.1 g every four hours OR **piperacillin-tazobactam** 4.5 g every six hours)

Patients with known hypersensitivity to penicillin may be treated with clindamycin plus a carbapenem. If carbapenems are not tolerated, clindamycin plus **vancomycin** or clindamycin plus **daptomycin** may be used.

**Tailored therapy** — Once a diagnosis of streptococcal TSS is established, treatment consists of clindamycin (900 mg IV every eight hours) in addition to **penicillin G** (4 million units IV every four hours). Penicillin is included together with clindamycin in case the infection is due to an organism that is resistant to clindamycin; this occurs in less than one percent of isolates in the United States [23]. Patients with known hypersensitivity to penicillin may be treated with clindamycin alone if the organism is known to be clindamycin-susceptible. In the setting of clindamycin resistance, a carbapenem may be used. It is important to note that an increasing number of GAS isolates with constitutive or inducible resistance to macrolide-lincosamide-streptogramin B (MLS) antibiotics, including clindamycin, have been identified in Europe [24]. There are no additive, synergistic, or antagonistic effects of clindamycin and penicillin in vitro.

**Duration of therapy** — There are no clinical studies addressing the optimal duration of antibiotic therapy in streptococcal TSS; the duration of antibiotic therapy should be individualized. Patients with bacteremia should be treated for at least 14 days. In patients with complicating deep-seated infections, such as necrotizing fasciitis, length of therapy depends on the clinical course and the adequacy of surgical debridement; therapy is usually continued for 14 days from the last positive culture obtained during surgical debridement.

**Adjunctive therapy** — Adjunctive therapies used for patients with streptococcal TSS include intravenous immune globulin (IVIG), hyperbaric oxygen, and anti–tumor necrosis factor (TNF) antibody.

**Intravenous immune globulin** — Data on the role of intravenous immune globulin for treatment of streptococcal TSS are limited, as discussed below [18,25-30]. In general, we favor administration of intravenous immune globulin for patients with streptococcal TSS; the rationale is to boost antibody levels via passive immunity in the setting of overwhelming infection.

One randomized trial including 21 patients compared IVIG to placebo in adults with streptococcal TSS (IVIG dosing was 1 g/kg on day one, and 0.5 g/kg on days two and three; all patients also received intravenous clindamycin and penicillin for at least 14 days) [30]. The mortality rates were 10 versus 36 percent, but statistical significance was not reached.

A subsequent prospective observational study compared IVIG therapy (23 patients) with placebo (44 patients); IVIG contributed to significantly improved survival (odds ratio 5.6, \( p = 0.03 \)) [31].

One retrospective study including 192 children with streptococcal TSS did not note improved outcomes associated with IVIG, although the overall mortality due to this disease is lower among children than adults [32]. Two other retrospective studies described 27 patients with streptococcal TSS treated with IVIG (median dose 2 g/kg) compared with historical controls [25,29]. Mortality was lower among patients treated with IVIG, but the use of historical controls posed potential difficulties in interpreting the results since fewer patients in the control group were managed with clindamycin or surgery.

Several mechanisms for IVIG in streptococcal TSS have been suggested, including neutralization of streptococcal toxins, inhibition of T-cell proliferation, and inhibition of other putative virulence factors such as TNF-alpha and interleukin (IL)-6 [25,33-37]. Some IVIG preparations contain neutralizing antibodies against several streptococcal toxins such as the pyrogenic exotoxins (SPEA, SPEB, SPEC, and MF), streptolysin O, and DNase B; specific antibody preparations are not commercially available [38]. (See “General principles in the use of immune globulin”.)

Differences between neutralizing activities have been observed in different batches of IVIG from different manufacturers. In one study, Vigam-S (obtained from plasma collected from donors in the United States) had consistently high inhibition against all superantigens, while European IVIG preparations had the lowest activity; an Australian preparation had intermediate activity [39].

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Other therapies — The use of hyperbaric oxygen has been reported in a small number of patients with streptococcal TSS [1]. There are no controlled data, and the efficacy of this treatment is not known. (See "Hyperbaric oxygen therapy").

Use of anti-TNF antibody has been studied in an animal model of streptococcal TSS with promising results [40]; further study is needed.

PROGNOSIS — The reported mortality rate for streptococcal toxic shock syndrome (TSS) ranges from 30 to 70 percent [2,3,26,41-43]. Mortality rates are lower in children than adults; one series including 144 children noted a mortality rate of 18 percent [44].

One retrospective including 66 patients with streptococcal TSS compared physical and laboratory findings of survivors (36 cases) and patients who died (30 cases) [43]. Patients who died had lower mean systolic blood pressure (99 versus 120 mm Hg), lower mean body temperature (37.0 versus 38.3°C), higher mean serum creatinine (3.0 versus 2.0 mg/dL), lower mean white blood cell count (1000 versus 16,000 cells per microl.), and lower platelet count (120,000 versus 170,000 cells per microl.).

Mortality due to streptococcal TSS is substantially higher than staphylococcal TSS. Streptococcal TSS is frequently associated with deep soft tissue infection, so source control can be difficult. In addition, streptococcal TSS occurs more frequently among patients with underlying medical conditions than staphylococcal TSS. (See "Staphylococcal toxic shock syndrome").

MANAGEMENT OF HOUSEHOLD CONTACTS — Group A Streptococcus (GAS) is a highly contagious organism; it has caused epidemics of pharyngitis and scarlet fever in schools, rheumatic fever in military recruits, and surgical wound infections in hospitalized patients. Close contacts of a case of invasive GAS infection have a high likelihood of becoming colonized with a virulent strain. The risk of developing a secondary case of toxic shock syndrome is very low but higher than for the general population [45].

The role of postexposure prophylaxis has not been studied, and the optimal approach is uncertain [46]. For highly susceptible individuals (such as immunocompromised individuals or patients with recent surgery) who are close household contacts of a patient with toxic shock syndrome, administration of prophylaxis with penicillin (250 mg orally four times daily for 24 to 48 hours) is reasonable. The goal is reduction in likelihood of a secondary infection rather than treatment of established infection.

SUMMARY AND RECOMMENDATIONS

- Management of streptococcal toxic shock syndrome (TSS) includes treatment of septic shock and associated complications, surgical debridement of infection (if feasible), and antimicrobial therapy. Early aggressive surgical intervention is critical. (See ‘Management’ above.)
- Empiric antimicrobial therapy should be initiated pending culture results; thereafter, antimicrobial therapy should be tailored accordingly. We recommend an empiric regimen consisting of clindamycin plus either a carbapenem or combination drug containing a penicillin plus beta-lactamase inhibitor (Grade 1B). (See ‘Empiric therapy’ above.)
- Once a diagnosis of streptococcal TSS is established, we recommend treatment with clindamycin (900 mg IV every eight hours) in addition to penicillin G (4 million units IV every four hours) (Grade 1B). The duration of antibiotic therapy depends on individual patient circumstances. (See ‘Empiric therapy’ above and ‘Tailored therapy’ above.)
- For patients with streptococcal TSS, we suggest administration of intravenous immune globulin (Grade 2B). Dosing consists of 1 g/kg day one, followed by 0.5 g/kg on days two and three. (See ‘Intravenous immune globulin’ above.)

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