Septic Cellulitis

Alexandra Eckhoff, DVM
Elizabeth G. Davis, DVM, PhD, DACVIM (Large Animal)
Kansas State University

ABSTRACT: Septic cellulitis is a severe, acute bacterial disease in which lesions disseminate along soft tissues. Infections commonly result from perivascular or intramuscular injections, penetrating skin wounds, blunt trauma, extension of a contiguous infection, or hematogenous spread of a septic condition. Clinical signs include sensitivity to palpation, swelling of the affected region, fever, depression, tachycardia, tachypnea, and lameness. A presumptive diagnosis of septic cellulitis can be made in horses based on history and clinical signs. Diagnostic testing involves hematology, ultrasonography, and fine-needle aspiration for cytologic and culture analysis. Successful therapy requires patient stabilization, administration of analgesics and appropriate broad-spectrum antibiotics, and supportive treatment. Secondary complications such as laminitis or immune-mediated hemolytic anemia can become life threatening. Successful treatment of septic cellulitis requires rapid recognition of the disease and effective antimicrobial therapy to reduce bacterial contamination and challenge.

Bacterial infections of soft tissues are classified based on the anatomic layers of affected tissues, such as the epidermis, dermis, subcutaneous fat, fascia, or muscle layers. Erysipelas is defined as an infection of the superficial layers of skin and cutaneous lymphatic vessels. Cellulitis denotes an infection of subcutaneous tissue, which spares the fasciae, whereas necrotizing fasciitis involves fascia and adipose tissue, including or excluding skin necrosis or myonecrosis. Myositis or myonecrosis are appropriate classifications if muscle layers are infected. Manifestations of soft tissue infections are difficult to clinically distinguish as independent conditions because it is likely for more than one tissue to be affected and for overlapping conditions to exist. Septic cellulitis can result from penetrating skin wounds as an extension of a contiguous foci of infection or via hematogenous spread from a distant source, particularly in areas affected by severe blunt trauma.1,4,5

CLINICAL MANIFESTATIONS

Septic cellulitis is typically characterized by severe, acute infection that may spread quickly along tissue planes. Affected horses are often febrile, depressed, and anorectic. Soft tissue swelling may initially be focal, but with disease progression, swelling becomes more diffuse and may affect the entire limb. The inflammatory response may develop hours to days following the initial insult, which may become diffuse or circumscribed. By 48 to 72 hours after the onset of clinical signs, serous or purulent discharge may exude from the area. In horses, the condition commonly affects a single limb with a tendency toward increased prevalence in hindlimbs.6,7 Cellulitis produces severe pain (horses commonly present with extreme sensitivity to
palpation) and severe lameness, potentially grade IV to V of V. Severe lameness may result in laminitis in the contralateral limb due to mechanical overload. With chronicity, tissue elasticity is commonly lost and pitting edema may take its place. Prolonged edema can lead to permanent sclerosis of the affected tissue(s)⁶,⁸ (Figure 1).

**Streptococcal and Staphylococcal Cellulitis**

Commonly identified etiologic agents isolated from affected soft tissue structures include *Staphylococcus* and *Streptococcus* spp. *Staphylococcus aureus* and group A *Streptococcus* spp can produce superantigens, which are low–molecular-weight proteins that may result in toxic shock syndrome. Although uncommon, this condition has been reported in a horse in association with *S. aureus* pneumonia.⁹ Extracellular toxins (α, β, γ, σ, and ε and toxic shock syndrome toxin-1) stimulate T lymphocytes to produce high levels of interleukins (ILs) and tumor necrosis factor as well as activate tissue macrophages. Activated phagocytes, in turn, produce inflammatory mediators, including tissue factor; tumor necrosis factor; IL-1, -6, and -8; platelet-activating factor; prostaglandins; leukotrienes; proteinases; and reactive oxygen intermediates, which potentiate thrombosis and inhibit fibrinolysis.¹⁰ Overzealous activation of T lymphocytes in toxic shock syndrome results from stimulation of the Vβ5 region of the T-cell receptor, which does not require antigen specificity, leading to nonspecific global T-cell activation.¹¹ Activated T cells release cytokines in large quantities that are responsible for the systemic changes associated with septic shock and multiorgan failure.²,¹² Clinical signs of toxic shock syndrome are similar to those observed in other systemic septic conditions, such as fever, rash accompanied by desquamation, hypotension, multiorgan dysfunction (e.g., hepatic and renal failure, adult respiratory distress syndrome), and coagulopathy.¹¹,¹³,¹⁴ Similar signs have been reported for group B streptococcal infections in infants (associated with childbirth) and adults with skin and soft tissue infections.¹³,¹⁵

Clinical signs related to septic cellulitis in horses and dogs appear similar to those in humans. Clinical manifestations of *Staphylococcus* spp infection in horses include localized heat, pain, non–weight-bearing lameness, pale mucous membranes, prolonged capillary refill time, fever, and depression with rapid deterioration and possible death within 48 hours after the onset of clinical signs. If the cellulitis is circumscribed, the subcutaneous tissue will appear yellow and gelatinous, with partial thrombosis of lymphatic and venous drainage. As the swelling becomes diffuse, lymphatic drainage ceases, and pustules begin to form. In dogs, *Staphylococcus intermedius* is the most commonly isolated agent,¹² whereas in horses, clinical infections can be caused by both *S. intermedius* and *S. aureus*.⁶,⁷

**Clostridial Cellulitis**

Septic cellulitis or fasciitis that progresses to myositis resulting from *Clostridium* spp is typically characterized by rapidly progressive (i.e., 6 to 72 hours), localized swelling with subcutaneous emphysema and toxemia, potentially resulting in death.¹⁶ Clostridial spores may
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be found dormant within healthy equine skeletal muscle, and soft tissue trauma must take place for clostridial myonecrosis to occur. This disease usually occurs following intramuscular injection with an irritating substance (e.g., ivermectin, antihistamine, flunixin meglumine, vaccines, vitamin B₁₂) or penetrating wounds, but soft tissue trauma has also been a cause. Septic cellulitis is unlikely to develop following intramuscular antibiotic administration. Localized pain and swelling in the region of drug (e.g., procaine penicillin, ceftiofur) administration is typically a local reaction to the drug depot, not a result of sepsis. Idiopathic forms of the disease in horses have been reported, but most studies refer to this form occurring only in ruminants and humans. In some instances, crepitant swelling develops and becomes increasingly painful within 48 hours of the primary insult and may extend to involve adjacent structures (Figure 2). If the disease progresses in an unrestricted manner, localized pain may diminish and the horse may become febrile, dehydrated, inappetent, dehydrated, tachycardic, and tachypneic. Immune-mediated hemolytic anemia can occur in conjunction with clostridial myositis and may be life threatening. A comprehensive description of clostridial myositis is beyond the scope of this article. (Other articles can provide more information.)

Other Forms of Cellulitis

Cellulitis resulting from Salmonella spp has been described in both humans and horses and is considered a rare form of extraintestinal infection resulting in 6% to 12% of all focal Salmonella spp infections in humans. This manifestation is usually found in human patients secondary to other debilitating conditions, such as immunosuppression, diabetes, human immunodeficiency virus infection, aplastic anemia, and sickle cell anemia. Salmonella spp infections manifest as abscess formation, dermatitis, cellulitis, pyomyositis, or necrotizing fasciitis. One report of limb cellulitis caused by Salmonella spp in a horse described clinical signs similar to those observed in other forms of cellulitis, including progressive swelling of the affected area eventually encompassing the entire limb as well as skin rupture with purulent discharge emanating from the lesions. The disease progressed in 5 days to include thrombosis of the digital arteries as a consequence of overwhelming sepsis, necessitating euthanasia of the horse.

Other bacterial organisms implicated in cellulitis include Corynebacterium pseudotuberculosis, Pneumococcus spp, Legionella spp, Aeromonas spp, Klebsiella spp, Peptococcus spp, Peptostreptococcus spp, Escherichia coli, Bacteroides spp, Clostridium spp, and Pasteurella spp. Polymicrobial isolates have also been reported in association with septic cellulitis in horses. Although uncommon, Rhodococcus equi has been identified as the causative agent of septic cellulitis in foals. Septic cellulitis as a clinical entity is nonspecific, and a variety of pathogens may be involved; therefore, determination of the inciting causative agent is important to allow the clinician to implement effective therapy.
A presumptive diagnosis of cellulitis can be based on history and clinical signs at presentation. Diagnostic evaluation should include a complete blood count, serum chemistry profile, a regional ultrasonographic examination, and fine-needle aspiration for cytologic and culture analysis. Interpretation of culture results should be weighed against response to therapy because diagnostic sample contamination may result from local skin flora during sample collection. In some cases, lameness and swelling are severe and the primary diagnostic differential is long-bone fracture, necessitating radiographic evaluation.

Laboratory findings that support a diagnosis of septic cellulitis include leukocytosis with a left shift, hypoalbuminemia (mild to moderate), and hyperfibrinogenemia. Elevated alkaline phosphatase, aspartate aminotransferase, blood urea nitrogen, and creatine kinase levels may also be found. Anemia, thrombocytopenia, basophilia, and hypocalcemia occur in some cases of septic cellulitis or fasciitis.

Ultrasoundographic examination of the affected region can reveal accumulation of subcutaneous fluid, and in the case of necrotic fasciitis, fluid or gas may exist deep within fascial planes. Fine-needle aspirations, biopsy specimens, and impression smear samples of affected tissue or exudate can be evaluated via Gram’s stain to aid in establishing the class of organism(s) associated with septic cellulitis. Aerobic and anaerobic cultures and antimicrobial sensitivity testing of the affected tissue or exudate are indicated to definitively identify the causative pathogens and direct antimicrobial therapy.

**THERAPEUTIC MANAGEMENT**

In some patients, systemic illness may require stabilization and support via intravenous fluid replacement, correction of electrolyte and acid–base imbalances, and administration of analgesics and broad-spectrum antibiotics. The likelihood of successful treatment of cellulitis improves with early disease recognition and prompt initiation of treatment. Debridement is necessary in severe cases of fasciitis to remove necrotic tissue, which decreases bacterial numbers and eliminates local toxin production by disrupting the anaerobic environment.

Because staphylococcal and streptococcal organisms are commonly involved, parenteral antibiotic therapy using β-lactam preparations (e.g., penicillin, ceftiofur, ampicillin; Table 1) is indicated. (An article regarding prudent antimicrobial use in horses is available.) Alternative options include tetracyclines, chloramphenicol, and metronidazole for their gram-positive anaerobic activity. However, penicillin remains the preferred treatment for group A streptococcal infections because susceptibility remains high, whereas strains resistant to tetracyclines, clindamycin, or erythromycin have been documented in association with human disease. Alternative antibiotics may be preferred in managing Clostridium spp infections because of rapid toxin production associated with bacterial death induced by β-lactam antibiotics. Alternative agents have good tissue penetration, and in vitro evidence suggests that metronidazole, tetracycline, chloramphenicol, and rifampin are superior with respect to efficacy, inhibition of toxin production, higher bactericidal rate, and postantibiotic effect. Because of production of β-lactamase enzymes that digest the β-lactam ring, this class of antibiotics is not recommended when Staphylococcus spp infections are suspected or confirmed. Aminoglycosides and enrofloxacin remain excellent therapeutic choices for horses with staphylococcal cellulitis. Adequate hydration is essential when selecting aminoglycosides because nephrotoxic effects are enhanced with dehydration and hypocalcemia. Effective antimicrobial therapy is a crucial component of successful management of horses with septic cellulitis. Duration of antimicrobial coverage depends on several factors, such as severity of disease, pathogen(s)
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Antimicrobial agents should be administered until complete resolution of clinical disease occurs, which may require several weeks of therapy.

Although advanced-stage necrotizing fasciitis is relatively easy to distinguish from cellulitis, these two disease processes can appear similar at presentation. Cellulitis generally responds more favorably to antibiotic therapy, whereas necrotizing fasciitis or myositis requires combination therapy composed of antibiotic therapy and surgical debridement of affected tissues. Therefore, if a patient is not responding favorably to appropriate antimicrobial coverage, surgical fenestration and debridement should be considered.

Additional supportive treatments include wound lavage, debridement of necrotic tissue, hydrotherapy, and pain management. During the acute stages of disease, supportive bandaging of the affected leg and contralateral limb are indicated. The use of compression bandages with topical hyperosmolar ointments can significantly aid in reducing local tissue swelling due to excess fluid accumulation. Leg massage is contraindicated during the acute stage of infection to avoid dissemination of infection but may be necessary to enhance resolution of the edema in later stages of the disease.

In our experience, persistent limb swelling may occur in approximately 30% of cases of severe cellulitis; therefore, rapid treatment aimed at reducing limb edema and clearing bacterial infection is paramount.

Pain management is particularly important because severe pain associated with septic cellulitis can lead to

Table 1. Antibiotics That May Be Administered in Horses with Septic Cellulitis

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage</th>
<th>Spectrum</th>
<th>Antimicrobial Activity</th>
<th>Susceptible Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>22,000–44,000 IU/kg q4–6h</td>
<td>Primarily gram-positive bacteria</td>
<td>Bactericidal</td>
<td>Corynebacterium, Clostridium, and Streptococcus spp</td>
</tr>
<tr>
<td>Ceftiofur</td>
<td>2.2–4.4 mg/kg q8–24h</td>
<td>Gram-positive and -negative bacteria</td>
<td>Bactericidal</td>
<td>E. coli; Proteus, Salmonella, and Klebsiella spp</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>11–20 mg/kg q6h</td>
<td>Gram-positive and -negative bacteria</td>
<td>Bactericidal</td>
<td>E.coli; Proteus and Salmonella spp</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>6.6 mg/kg q24h</td>
<td>Gram-negative bacteria</td>
<td>Bactericidal</td>
<td>Enterobacteriaceae and Staphylococcus spp</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>6–10 mg/kg q12–24h</td>
<td>Gram-positive and -negative bacteria</td>
<td>Bacteriostatic</td>
<td>Ehrlichia, Staphylococcus, and Streptococcus spp</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>33–50 mg/kg q6h</td>
<td>Gram-positive and -negative bacteria</td>
<td>Bacteriostatic</td>
<td>Corynebacterium, Salmonella, Clostridium, and Staphylococcus spp</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>15–25 mg/kg q6–8h</td>
<td>Gram-positive anaerobes</td>
<td>Bactericidal</td>
<td>Streptococcus and Clostridium spp</td>
</tr>
<tr>
<td>Rifampin</td>
<td>5–10 mg/kg q12h</td>
<td>Gram-positive anaerobes</td>
<td>Bactericidal</td>
<td>Staphylococcus spp and R. equi</td>
</tr>
<tr>
<td>Enrofloxacin</td>
<td>5–7.5 mg/kg q24h</td>
<td>Gram-negative bacteria</td>
<td>Bactericidal</td>
<td>Enterobacteriaceae, Staphylococcus spp, and Pseudomonas aeruginosa</td>
</tr>
</tbody>
</table>

*aDosage recommended by authors.

*bVariable susceptibility caused by acquired resistance.
persistent tachycardia, minimal weight bearing, and altered gastrointestinal (GI) motility. Sedatives and analgesics (e.g., detomidine, butorphanol, xylazine) can initially be used to control pain but should not be used continuously because they may alter GI motility patterns. NSAID therapy (e.g., phenylbutazone [2.2 to 4.4 mg/kg IV or PO q12h], flunixin meglumine [1.1 mg/kg IV or PO q12h]) may provide effective analgesia to a patient with mild to moderate disease. However, in cases of severe musculoskeletal pain or if GI ulcers have developed, alternative modes of analgesia should be considered. Alternative options include administration of epidural analgesia (e.g., xylazine, morphine) to treat hindlimb disease or topical application of fentanyl patches (one on each forelimb; 100 μg q72h). In many cases, when severe pain exists, the use of multiple pharmacologic agents provides superior analgesia compared with suprapharmacologic doses of one analgesic class. Secondary complications of limb cellulitis include laminitis of the affected or contralateral limb, large areas of skin loss, bacteremia, osteomyelitis, septic arthritis, and endocarditis. Complications are best managed by prompt identification to allow implementation of appropriate therapeutic management.

CONCLUSION
Localized soft tissue infection in horses can progress rapidly to involve the entire limb. Clinical disease associated with septic cellulitis typically involves severe pain, lameness, and swelling in the affected region, progressing to systemic illness. Early recognition of localized cellulitis based on the appearance of the lesion, degree of pain, and systemic involvement combined with appropriate antimicrobial and supportive therapy offers the best chance of survival and recovery.

REFERENCES


**ARTICLE #2 CE TEST**

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1. **Which has not been associated with septic cellulitis?**
   a. vaccination
   b. blunt trauma
   c. ingestion of spores
   d. hematogenous spread

2. **Which injectable has not been associated with myositis?**
   a. ivermectin
   b. vitamin B₁₂
   c. flunixin meglumine
   d. antibiotics

3. **The most commonly isolated pathogens in patients with septic cellulitis are**
   a. Staphylococcus, Streptococcus, and Clostridium spp.
   b. E.coli as well as Chlamydia and Salmonella spp.
   c. R. equi as well as Brucella and Clostridium spp.
   d. Ehrlichia, Staphylococcus, and Streptococcus spp.

4. **The lethal extracellular toxins associated with staphylococcal infection interact with which of the following leukocyte cell types?**
   a. neutrophils
   b. basophils
   c. eosinophils
   d. lymphocytes

5. **Clostridial infection and related cellulitis or myonecrosis most commonly result from clostridial spores**
   a. originating from iatrogenic inoculation.
   b. that have been dormant within host muscle tissue.
   c. that have been ingested.
   d. that have been inhaled.

6. **An important difference between septic cellulitis and necrotizing fasciitis is that septic cellulitis**
   a. always resolves while necrotizing fasciitis is always lethal.
   b. requires antibiotics while necrotizing fasciitis requires antibiotics and surgical debridement.
   c. responds to fluid therapy and topical antibiotics while necrotizing fasciitis responds to injectable antibiotics.
   d. has a higher mortality rate than does necrotizing fasciitis.

7. **Hematologic changes characteristic of septic cellulitis include**
   a. leukocytosis and normal fibrinogen concentration.
   b. leukopenia and hyperfibrinogenemia.
   c. leukopenia and normal fibrinogen concentration.
   d. leukocytosis and hyperfibrinogenemia.

8. **The typical timeframe for death resulting from septic cellulitis is __________ after the onset of clinical signs.**
   a. 12 to 24 hours
   b. 48 to 72 hours
   c. 72 to 96 hours
   d. 2 to 3 weeks
9. Which statement regarding cellulitis caused by *S. aureus* infection is correct?
   a. *S. aureus* has not been associated with septic cellulitis in horses.
   b. It is most effectively managed with parenteral gentamicin or enrofloxacin.
   c. It responds well to oral β-lactam antibiotics.
   d. It responds well to parenteral penicillin therapy.

10. Which serum chemistry profile finding(s) would be unlikely in a patient with septic cellulitis?
    a. hypoalbuminemia and thrombocytopenia
    b. azotemia and an elevated creatine kinase level
    c. hypercalcemia and a decreased alkaline phosphatase level
    d. No abnormalities are likely to be identified in horses with septic cellulitis.