Clostridial myonecrosis

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INTRODUCTION

Clostridial myonecrosis (gas gangrene) is a life-threatening muscle infection that develops either contiguously from an area of trauma or hematogenously from the gastrointestinal tract with muscle seeding. Early recognition and aggressive treatment are essential.

There are two major presentations of clostridial gas gangrene: traumatic and spontaneous. Traumatic gas gangrene is most commonly caused by *Clostridium perfringens*; spontaneous gangrene is most commonly caused by *Clostridium septicum*.

Issues related to necrotizing muscle infections due to *Clostridium* species will be reviewed here. Issues related to streptococcal necrotizing myositis and infections involving the skin and fascia are discussed separately. (See "Necrotizing soft tissue infections".)

SPECTRUM OF CLOSTRIDIAL INFECTIONS

Clostridium species are widespread in nature due to their ability to form endospores. They are commonly found in soil and marine sediments as well as human and animal intestinal tracts. Categories of clostridial soft tissue infections include wound contamination, anaerobic cellulitis, myonecrosis (gas gangrene), and necrotizing fasciitis [1].

- Wound contamination with soil containing clostridial spores or vegetative organisms may occur. In one study, for example, 30 to 80 percent of open traumatic wounds were contaminated with clostridial species [2]. However, such contamination in the absence of devitalized tissue does not necessarily lead to infection.

- Anaerobic cellulitis requires an anaerobic niche such as devitalized tissue to support the growth of *C. perfringens* or other clostridial strains. Gas is produced locally and extends along fascial planes; bacteremia and invasion of healthy tissue (including muscle) does not occur. Mortality is low with appropriate management, including prompt removal of the devitalized tissue [1].

- Myonecrosis (clostridial gas gangrene) may be distinguished from the above infections by the progressive invasion and destruction of healthy muscle and other soft tissues [2]. There are two major presentations of clostridial gas gangrene: traumatic and spontaneous.

CLOSTRIDIAL MYONECROSIS

Myonecrosis (clostridial gas gangrene) is characterized by rapidly progressive invasion and destruction of healthy muscle and other soft tissues. Traumatic gas gangrene is most commonly caused by *C. perfringens*; spontaneous gangrene is most commonly caused by the more aerotolerant *C. septicum*.

Traumatic gas gangrene — Traumatic wounds with vascular compromise (particularly deep penetrating injuries such as knife wounds, gunshot wounds, and crush injuries) create an anaerobic environment that is ideal for proliferation of clostridia. Traumatic injury accounts for about 70 percent of gas gangrene cases, and about 80 percent of these are caused by *C. perfringens* [1]. Other pathogens include *C. septicum*, *C. novyi*, *C. histolyticum*, *C. bifermentans*, *C. tertium*, and *C. fallax*.

Gas gangrene was a common infection in the American Civil War, World War I, and World War II due to delayed treatment of injuries. In modern times, evacuation to medical facilities, rapid vascular repair, and antibiotic treatment have dramatically reduced the incidence of this disease. Gas gangrene caused by *C. perfringens* continues to occur among victims of natural disasters where evacuation and treatment are delayed. As an example, following an earthquake in China, the average time from injury to medical treatment was 3.5 days, and 20 percent of patients with open wounds developed gas gangrene caused by *C. perfringens*; mortality was 50 to 80 percent [3].

Conditions associated with traumatic gas gangrene include:

- Gunshot wounds, knife wounds
- Compound fractures, crush injuries
- Bowel and biliary tract surgery
- Abortion
- Retained placenta
- Prolonged rupture of the membranes
- Intrauterine fetal demise
- Intramuscular injection
- Black tar heroin injection (skin popping) [4]

Traumatic gas gangrene may have other microbes isolated from the site of trauma; however, clostridia are the major agents causing destruction of healthy tissue.

Recurrent gas gangrene due to *C. perfringens* has been described in individuals with minor trauma at sites of previous gas gangrene [5]. Such cases are likely attributable to the germination of residual *C. perfringens* spores, which can remain quiescent in tissues not adequately debrided for decades.

Pathogenesis — Trauma introduces organisms (vegetative or spore forms) directly into deep tissue. If trauma compromises the blood supply, an anaerobic environment forms with low oxidation-reduction potential and acidic pH, which is optimal for growth of clostridial organisms [1,2]. Necrosis of tissue can develop within hours of injury and progresses rapidly (inches per hour) in the absence of treatment.

In gas gangrene, muscle necrosis is severe, and polymorphonuclear leukocytes (PMNs) are notably absent from infected tissues. This is in contrast with soft tissue infections caused by organisms such as *Staphylococcus aureus*, in which significant influx of PMNs localizes the infection without adjacent tissue or vascular destruction. In clostridial infection, PMNs arriving at the site of infection adhere to and accumulate along the endothelium of capillaries, small arterioles, and postcapillary venules but do not cross the vascular endothelium into infected tissue [6,7].

Many extracellular toxins are produced by *C. perfringens*; of these, alpha and theta toxins have been implicated in pathogenesis:

- Alpha toxin is a hemolytic toxin with both phospholipase C (PLC) and sphingomyelinase activities. Two independent studies have identified alpha toxin as an essential toxin in disease. First, genetic interruption of the alpha toxin gene in *C. perfringens* rendered the

organism avirulent in a mouse myonecrosis model [1]. Complementation of the chromosomal mutation with a recombinant plasmid carrying a wild-type gene fully restored ability to cause disease. Second, vaccination with the C-terminal domain of alpha toxin (amino acids 247 to 370) protected mice from experimental *C. perfringens* infection in part by improving tissue perfusion and restoring the tissue inflammatory response [8,9].

- Theta toxin (also known as perfringolysin O) is a member of the cholesterol-dependent cytolysin family that includes streptolysin O, pneumolysin, listeriolysin, septicolysin, and others [10]. These pore-forming toxins contain a conserved amino acid motif. Theta toxin contributes to pathogenesis by its effects on cells of the vascular and immune systems [11-13]. However, theta toxin is not essential in causing mortality since isogenic mutant strains lacking an intact theta toxin structural gene (*pfoA*) remained lethal in the mouse myonecrosis model [1].

Molecular and animal studies have shown that alpha toxin is largely responsible for both the widespread tissue necrosis and the characteristic absence of a tissue inflammatory response. Alpha toxin potently stimulates platelet aggregation and upregulates adherence molecules on PMNs and endothelial cells. Experimental intramuscular alpha toxin injection causes a rapid, irreversible decline in muscle blood flow and concomitant ischemic necrosis of tissue due to the formation of occlusive intravascular aggregates of activated platelets, leukocytes, and fibrin. The perfusion deficits expand the anaerobic environment and contribute to the rapidly advancing margins of tissue destruction characteristic of clostridial gas gangrene.

In addition, large heterotypic aggregates of activated platelets and PMNs reduce the ability of PMNs to cross the endothelial cell barrier into infected tissues. These processes are largely dependent on alpha toxin-induced activation of the platelet fibrinogen receptor, glycoprotein IIb/IIIa [14,15], suggesting that platelet glycoprotein inhibitors (eg, eptifibatide, abciximab) may be therapeutic for maintaining tissue blood flow. Thus, the major mechanism explaining the absence of PMNs in tissue is sequestration within the adjacent vasculature. Since alpha and theta toxin also are cytotoxic to PMNs in high concentrations, the small numbers of PMNs that do migrate into tissue are likely destroyed by these toxins.

Shock associated with gas gangrene may be attributable to both direct and indirect effects of alpha and theta toxins. Alpha toxin directly suppresses myocardial contractility and may contribute to profound hypotension via a sudden reduction in cardiac output [16,17]. In experimental models, theta toxin causes markedly reduced systemic vascular resistance combined with a markedly increased cardiac output (ie, "warm shock") [16,17]. This likely occurs via induction of endogenous mediators such as prostacyclin, platelet activating factor, and other lipid autocoids that cause vasodilation [18].

Patients with gram-negative sepsis compensate for hypotension by markedly increasing cardiac output. However, this adaptive mechanism may not be possible in the setting of shock due to *C. perfringens* given the negative inotropic effect of alpha toxin [16]. The roles of other endogenous mediators such as cytokines (eg, tumor necrosis factor, interleukin-1, interleukin-6) and vasodilators (such as bradykinin) have not been fully elucidated. (See "Pathophysiology of sepsis".)

Clinical manifestations — Traumatic gas gangrene usually presents with sudden onset of severe pain at the site of surgery or trauma [2,19]. The mean incubation period is less than 24 hours (range 6 hours to several days) and depends on the size of the bacterial inoculum and the extent of vascular compromise. Pain is likely related to toxin-mediated ischemia.

The skin over the infected area initially may appear pale then rapidly develops a bronze appearance, followed by purple or red discoloration. The skin becomes tense and exquisitely tender. Overlying bullae may be clear, red, blue, or purple.

Signs of systemic toxicity develop rapidly including tachycardia and fever, followed by shock and multiorgan failure. In one series, shock was present in 50 percent of patients at the time of presentation to the hospital [20].

Bacteremia occurs in about 15 percent of cases and may be associated with brisk intravascular hemolysis (picture 1). One case report described a patient whose hematocrit dropped from 37 to 0 percent over a 24-hour period; despite transfusion with 10 units of packed red blood cells over four hours, the hematocrit never exceeded 7 percent [21]. Both alpha and theta toxins appear to contribute to the marked intravascular hemolysis based upon experimental in vitro studies performed with recombinant toxins [17,22].

Bacteremia with *C. perfringens* can occur transiently in patients without gas gangrene, although the majority of *C. perfringens* and *C. septicum* blood isolates are associated with clinically significant infection [23,24].

Additional complications of clostridial myonecrosis include jaundice, renal failure, hypotension, and liver necrosis. Renal failure is largely due to the combined effects of hypotension, hemoglobinuria, and myoglobinuria. Bacterial toxins may also exert a direct effect on renal tubular cells.

Diagnosis — Pain at a site of traumatic injury together with signs of systemic toxicity and gas in the soft tissue support the diagnosis of gas gangrene. Physical evidence of crepitus in the soft tissue is the most sensitive and specific finding on clinical examination [25].

Radiographic imaging with computerized tomographic (CT) scan or magnetic resonance imaging (MRI) can reveal gas in deep tissues. Early in the course of infection, CT and MRI are useful for determining if the infection is localized or spreading along fascial planes.

Blood (both aerobic and anaerobic bottles) and tissue cultures should be obtained; definitive diagnosis of gas gangrene requires demonstration of large gram-variable rods at the site of injury (picture 2 and picture 3). Clostridia can appear both gram positive and gram negative when stained directly from infected tissues but stain as gram-positive rods when obtained from culture media [26,27]. Drainage from surgical procedures characteristically lacks frank pus. Histopathology demonstrates widespread tissue destruction and the presence of organisms but an absence of neutrophils in the tissue.

Surgical exploration in the setting of traumatic gas gangrene typically demonstrates muscle that does not bleed or contract when stimulated. Muscle tissue is grossly edematous and may have reddish-blue to black discoloration. Microscopic evaluation of biopsy material invariably demonstrates organisms among degenerating muscle bundles and a characteristic absence of acute inflammatory cells (picture 4) [2,28]. In the presence of muscle necrosis, necrosis of skin, fat, subcutaneous tissue, and fascia may also be present.

Needle aspiration or punch biopsy provides an etiologic diagnosis in at least 20 percent of cases. However, these techniques should not replace thorough surgical exploration and debridement of the infected site with retrieval of specimens for Gram stain and culture.

Treatment — Treatment of traumatic gas gangrene consists of surgical debridement, antibiotic therapy, and supportive measures. Patients with trauma who have not received tetanus immunization for 5 years should receive a booster vaccine against tetanus.

- **Surgical debridement** − Prompt, aggressive, and thorough surgical inspection and debridement of devitalized tissue are mandatory to improve survival, preserve limbs, and prevent complications [29,30]. Initial aggressive debridement of devitalized tissue can reduce the risk of gas gangrene in contaminated deep wounds. Maintaining vascular integrity is crucial; prolonged application of tourniquets should be avoided, and traumatic wounds such as compound fractures should not be surgically closed prematurely [31]. Presence of foreign material in a wound site increases the risk for gangrene. In general, multiple surgical debridement procedures over the course of several days may be required. Other surgical interventions may also be warranted depending on individual circumstances (such as hysterectomy in patients with postpartum clostridial infection) [32].

- **Antibiotic therapy** − Pending definitive etiologic diagnosis, broad-spectrum empiric antibiotic treatment is warranted to cover group A *Streptococcus*, *Clostridium* species, and

mixed aerobes and anaerobes. In the setting of polymicrobial infection, *Clostridium* is presumed to be a significant pathogen. Piperacillin-tazobactam (4.5 g intravenously every eight hours) PLUS clindamycin (900 mg intravenously every eight hours) is the preferred option. Carbapenems are an acceptable alternative to piperacillin-tazobactam.

Definitive antibiotic therapy should consist of the combination of penicillin (3 to 4 million units intravenously every four hours) plus clindamycin (900 mg intravenously every eight hours) or tetracycline (500 mg intravenously every six hours) [33]. The combination of penicillin and clindamycin is the most favorable based on animal models [34]; clinical trials comparing the efficacy of these agents in humans have not been performed. For patients with penicillin allergy, clindamycin can be used alone.

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.

Antibiotic agents with excellent in vitro activity against *C. perfringens* include penicillin, clindamycin, tetracycline, chloramphenicol, metronidazole, and a number of cephalosporins. Studies in mice suggest that clindamycin has significantly greater activity than penicillin in experimental gas gangrene [29,30,34,35]. Other agents with greater efficacy than penicillin in experimental myonecrosis models include tetracycline, erythromycin, rifampin, chloramphenicol, and metronidazole [34,35]. The superior in vivo efficacy of clindamycin and tetracycline in these studies may be related to the ability of these agents to inhibit toxin synthesis [36]. The diminished efficacy of penicillin may be related to ongoing toxin production by organisms that survive in filamentous form, due to the action of penicillin on cell wall formation [36].

These recommendations are in agreement with the Infectious Diseases Society of America (IDSA) guidelines for the treatment of skin and soft tissue infections [37].

Although *C. perfringens* remains largely susceptible to first-line antibiotics, antibiotic resistance has been reported, highlighting the importance of good anaerobic microbiology and susceptibility testing to guide optimal clinical management decisions for clostridial infections. Reports from the United Kingdom, Spain, Canada, and Taiwan found clindamycin-resistant *C. perfringens* from various sites [38-42]. A 2019 study from Iran found that 21.2 percent of *C. perfringens* isolates were resistant to penicillin [43]. In a two-year prospective study from Canada, 14.2 percent of clostridium species other than *C. perfringens* were penicillin resistant and 21.6 percent clindamycin resistant [42].

- **Adjunctive measures** − The use of hyperbaric oxygen (HBO) is controversial, largely due to the lack of data from randomized controlled trials in humans and to divergent results from studies in animals. Some nonrandomized studies have reported good results with HBO therapy when combined with antibiotics and surgical debridement [44]. Patients that are hemodynamically unstable may not be candidates for HBO therapy. Experimental studies in animals have failed to demonstrate therapeutic efficacy of HBO alone or the ability of HBO to enhance antibiotic efficacy [45]. The absolute necessity of surgical debridement should not be delayed while pursuing HBO treatment. (See "Hyperbaric oxygen therapy".)

  Therapeutic strategies directed against toxin activity in vivo may be valuable adjuncts to traditional antimicrobial regimens. Antitoxin for passive immunotherapy is not available; active immunization of experimental animals with the cell-binding domain of alpha toxin is 100 percent protective against a lethal challenge with *C. perfringens* [8,9]. Future treatment strategies may include attenuation of toxin-induced vascular leukostasis and resultant tissue injury by targeting endogenous proadhesive molecules and reducing duration and severity of shock via anti-cytokine molecules.

Prognosis — The prognosis for gas gangrene of an extremity is more favorable than gas gangrene of the trunk or visceral organs, since gangrene of an extremity may be debrided more readily [20,29,30]. Recurrent gas gangrene due to *C. perfringens* has been described in individuals with minor trauma at sites of previous gas gangrene [5].

Patients with associated bacteremia and intravascular hemolysis have the greatest likelihood of progressing to shock and death. Mortality is highest for patients in shock at the time of diagnosis. In a series of 139 patients treated with antibiotics, surgery, and hyperbaric oxygen, 67 were in shock at admission, and all deaths (27 patients) occurred in this subset; overall survival was 81 percent [20].

Spontaneous gas gangrene — Spontaneous gas gangrene generally occurs via hematogenous seeding of muscle with bacteria (usually *C. septicum*) from a gastrointestinal tract portal of entry. Gastrointestinal lesions are commonly known or undiagnosed adenocarcinoma of the colon. (See "Clinical presentation, diagnosis, and staging of colorectal cancer".)

Spontaneous gas gangrene can also occur in patients who have congenital or cyclic neutropenia and among patients with prior radiation therapy to the abdomen. The diagnosis of spontaneous gas gangrene is frequently missed or delayed because it is not entertained. (See 'Clinical manifestations' below.)

C. septicum has been transmitted from contaminated musculoskeletal allografts (tendons, menisci, femoral condyles) harvested from cadaveric tissues. In a report of 14 such cases, all came from a single tissue bank in which the rate of infection was 0.07 percent among more than 20,000 allografts [46].

C. tertium has been associated with spontaneous myonecrosis. It can grow aerobically so may be mistaken for a contaminant such as a diphtheroid or *Bacillus* species [29,30]. The organism's resistance to penicillin, cephalosporins, and clindamycin may facilitate survival in the gastrointestinal tract, especially in patients receiving broad-spectrum antibiotics [29].

Pathogenesis — *C. septicum* can grow in normal tissues; it does not require anaerobic conditions. The presence of a gastrointestinal lesion facilitates entry of the organism into the bloodstream and then into other tissues [1].

C. septicum produces multiple exotoxins, including [1]:

- Alpha toxin (a lethal, hemolytic, necrotizing toxin)
- Beta toxin (DNase)
- Gamma toxin (hyaluronidase)
- Delta toxin (septicolysin, an oxygen labile hemolysin)
- A protease
- A neuraminidase

The mechanism by which the alpha toxin of *C. septicum* contributes to pathogenesis is unknown; unlike the alpha toxin of *C. perfringens*, the alpha toxin of *C. septicum* does not possess phospholipase activity [47].

Clinical manifestations — Spontaneous gas gangrene usually presents with abrupt onset of severe muscle pain. Occasionally, heaviness or numbness is reported [1,2,48-50]. In some patients, the first manifestation may be confusion or malaise.

Infection progresses rapidly with development of edema and bullae filled with clear, cloudy, hemorrhagic, or purplish fluid. The skin around the bullae has a purple hue, perhaps reflecting vascular compromise resulting from bacterial toxins diffusing into surrounding tissues [48]. Histopathology of muscle and connective tissues demonstrates cell lysis and gas formation; inflammatory cells are absent [48].

Predisposing factors include [48-50]:

- Colonic malignancy
- Inflammatory bowel disease

- Diverticulitis
- Gastrointestinal surgery
- Leukemia
- Lymphoproliferative disorders
- Chemotherapy
- Neutropenia
- Radiation therapy
- Advanced AIDS
- Necrotizing enterocolitis, cecitis, or distal ileitis

Diagnosis — Fever and severe pain in an extremity (in the absence of trauma) should raise suspicion for spontaneous gas gangrene. Distinguishing spontaneous gas gangrene due to clostridia from streptococcal myositis may be difficult [48]. The presence of tissue crepitus favors clostridial infection (image 1) [51,52]. Gas within the soft tissue can also be detected by radiography, CT scan, or MRI.

Definitive diagnosis of spontaneous gas gangrene requires demonstration of large gram-variable rods at the site of injury. Gram stain of bullous fluid may be particularly useful. Blood cultures should also be obtained since bacteremia in *C. septicum* gangrene usually precedes cutaneous manifestations by several hours.

Surgical findings are as described for traumatic gas gangrene (picture 2 and picture 3 and picture 4). (See 'Diagnosis' above.)

Treatment — Treatment of spontaneous gas gangrene consists of early surgical debridement and antibiotic therapy. Urgent, thorough surgical debridement is mandatory to improve survival, preserve limbs, and prevent complications [29,30]. Multiple surgical debridements may be required.

Pending definitive etiologic diagnosis, broad-spectrum empiric antibiotic treatment is warranted to cover group A *Streptococcus*, *Clostridium* species, and mixed aerobes and anaerobes. In the setting of polymicrobial infection, *Clostridium* is presumed to be a significant pathogen. The preferred regimen is piperacillin-tazobactam (4.5 g intravenously every eight hours) PLUS clindamycin (900 mg intravenously every eight hours).

Definitive antibiotic therapy for treatment of spontaneous gas gangrene due to *C. septicum* should consist of the combination of penicillin (3 to 4 million units intravenously every four hours) plus clindamycin (900 mg intravenously every eight hours) or tetracycline (500 mg intravenously every six hours).

This approach is extrapolated from the treatment of traumatic gas gangrene due to *C. perfringens* and is based on animal models; no human trials have compared the efficacy of antibiotics for treatment of spontaneous gas gangrene. Antibiotic agents with excellent in vitro activity against both *C. septicum* and *C. perfringens* include penicillin, tetracycline, erythromycin, clindamycin, chloramphenicol, and metronidazole. Agents that inhibit exotoxin production would likely have greater efficacy in vivo than cell wall–active antibiotics. (See 'Treatment' above.)

C. tertium is resistant to penicillin, cephalosporins, and clindamycin [29]. Appropriate therapy for *C. tertium* infection is vancomycin (table 1) or metronidazole (500 mg intravenously every 8 hours).

Patients who survive spontaneous gangrene should have colonoscopy to rule out associated pathology of the gastrointestinal tract.

Prognosis — The mortality of spontaneous gangrene ranges from 67 to 100 percent [53,54]. The majority of deaths occur within 24 hours of onset. Risk factors for a fatal outcome include underlying malignancy and immunocompromised state.

DIFFERENTIAL DIAGNOSIS

Other clinical entities that must be distinguished from clostridial myonecrosis include:

- Necrotizing infection due to group A *Streptococcus* – Clostridial myonecrosis and necrotizing infection due to group A *Streptococcus* can be difficult to distinguish; both involve rapid and severe tissue destruction with systemic toxicity (table 2). The presence of tissue crepitus on clinical examination or radiographic imaging favors clostridial infection; the two are distinguished by Gram stain and bacteriologic culture. (See "Necrotizing soft tissue infections".)

- Wound infection due to *Vibrio vulnificus* – Both clostridial myonecrosis and infection due to *V. vulnificus* can occur following development of a traumatic wound; *V. vulnificus* generally occurs following exposure to sea water. The diagnosis of each is established by Gram stain and culture. (See "Vibrio vulnificus infection".)

- Pyomyositis (muscle abscess, usually caused by *S. aureus*) – Like clostridial myonecrosis, pyomyositis can occur following trauma or can develop spontaneously. They differ in that pyomyositis is not routinely associated with systemic toxicity or the presence of gas in

tissue on radiographic imaging. The two are distinguished by Gram stain and culture. (See "Primary pyomyositis".)

- Viral myositis – Viral infection such as acute influenza type A can produce skeletal muscle injury. It differs from clostridial myonecrosis in that the muscle pain is diffuse rather than localized, and it is not routinely associated with systemic toxicity or gas in tissues. (See "Seasonal influenza in adults: Clinical manifestations and diagnosis", section on 'Myositis and rhabdomyolysis'.)

- Rhabdomyolysis (muscle necrosis) – Both rhabdomyolysis and clostridial myonecrosis are associated with muscle pain; rhabdomyolysis has many causes including trauma, drugs, toxins, and metabolic disorders. Clostridial necrosis is distinguished by the presence of gas in tissues and Gram stain findings. (See "Rhabdomyolysis: Epidemiology and etiology".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Skin and soft tissue infections".)

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 5^{th} to 6^{th} 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 10^{th} to 12^{th} 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 topic (see "Patient education: Gangrene (The Basics)")

SUMMARY AND RECOMMENDATIONS

- Clostridial myonecrosis (gas gangrene) is a life-threatening muscle infection that develops either contiguously from an area of trauma (usually due to *Clostridium perfringens*) or hematogenously from the gastrointestinal tract with muscle seeding (usually due to *Clostridium septicum*). (See 'Introduction' above.)

- Traumatic wounds with vascular compromise (particularly deep penetrating injuries such as knife wounds, gunshot wounds, and crush injuries) create an anaerobic environment that is ideal for proliferation of clostridia. Most such cases are caused by *C. perfringens*. (See 'Traumatic gas gangrene' above.)

- Gas gangrene usually presents with sudden onset of severe muscle pain. Initially, the skin may appear pale and then rapidly develops a bronze appearance, followed by purple or red discoloration. The skin becomes tense and exquisitely tender and may have overlying bullae. Signs of systemic toxicity develop rapidly, including fever and tachycardia, followed by shock and multiorgan failure. (See 'Clinical manifestations' above.)

- Definitive diagnosis of gas gangrene requires demonstration of large, gram-variable rods at the site of injury. Histopathology demonstrates characteristic absence of acute inflammatory cells. Gas in the soft tissue may be observed at the bedside and/or radiographically. (See 'Diagnosis' above.)

- Treatment of traumatic gas gangrene consists of aggressive and thorough surgical debridement together with antibiotic therapy. We suggest the following antibiotic regimen: penicillin (3 to 4 million units intravenously every four hours) together with clindamycin (900 mg intravenously every eight hours) (**Grade 2B**). For patients with penicillin allergy, clindamycin can be used alone.

- The value of hyperbaric oxygen (HBO) is controversial, though some nonrandomized observational studies have reported good results with HBO in combination with antibiotics and surgical debridement. However, the absolute necessity of surgical intervention should not be delayed while pursuing HBO therapy. (See 'Treatment' above.)

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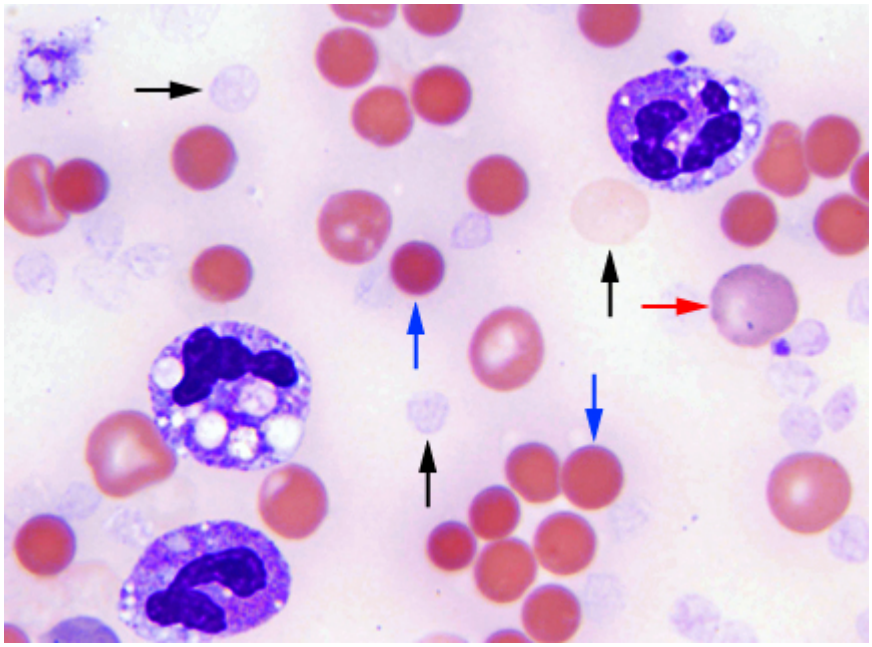
Topic 7672 Version 31.0

GRAPHICS

Intravascular hemolysis due to *Clostridium perfringens* sepsis

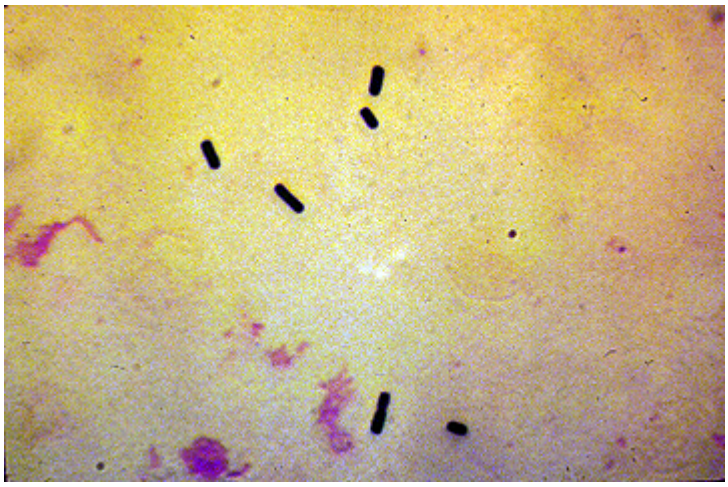


This is a peripheral blood smear from a patient with severe intravascular hemolysis due to sepsis with *Clostridium perfringens*. Neutrophils show toxic changes, including toxic granulation and vacuoles. There is an increased number of spherocytes (blue arrows) and polychromatophilic red cells (ie, reticulocytes [red arrow]). The major finding on this slide is the large number of red blood cell ghosts (black arrows), due to the intravascular lysis of red cells from the phospholipase and other lytic enzymes elaborated by the clostridial organisms.

Kindly provided by Dr. German Pihan, Department of Pathology, Beth Israel Deaconess Medical Center, Boston, MA.

Graphic 53404 Version 5.0

Clostridium perfringens Gram stain

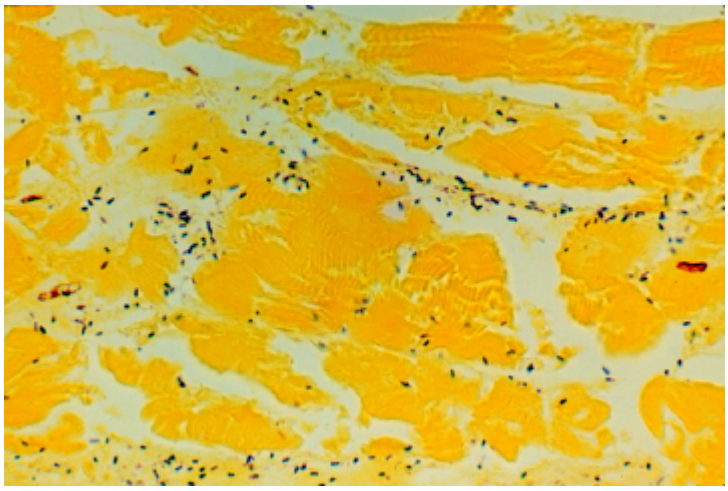


Gram stain of exudate from a bulla at the site of injection of intravenous drugs (x1000) shows large gram-positive bacilli and the absence of leukocytes. *Clostridium perfringens* grew anaerobically from this specimen on blood agar. Clostridial infection may produce cellulitis or involve deeper tissues, as in gas gangrene.

Courtesy of Harriet Provine.

Graphic 54494 Version 4.0

Clostridia in muscle

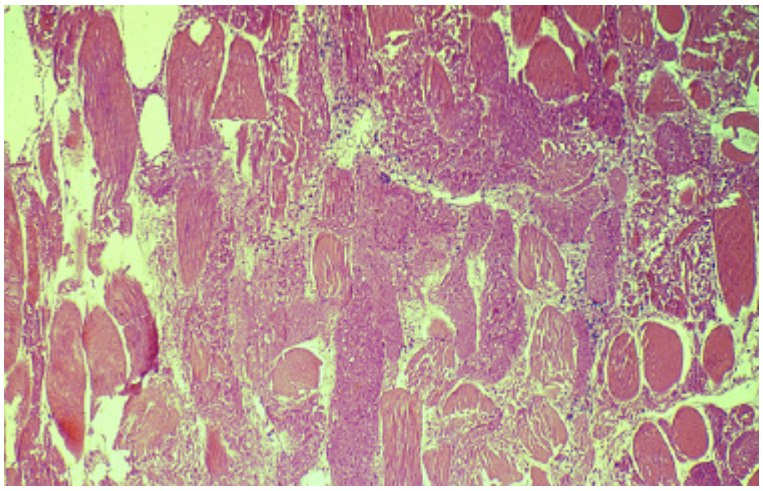


Tissue Gram stain of muscle biopsy (x400) from a patient with gas gangrene shows numerous gram-positive bacilli. *Clostridium perfringens* grew from this specimen.

Courtesy of Stephen Calderwood, MD.

Graphic 80492 Version 4.0

Necrotic muscle with clostridial gas gangrene

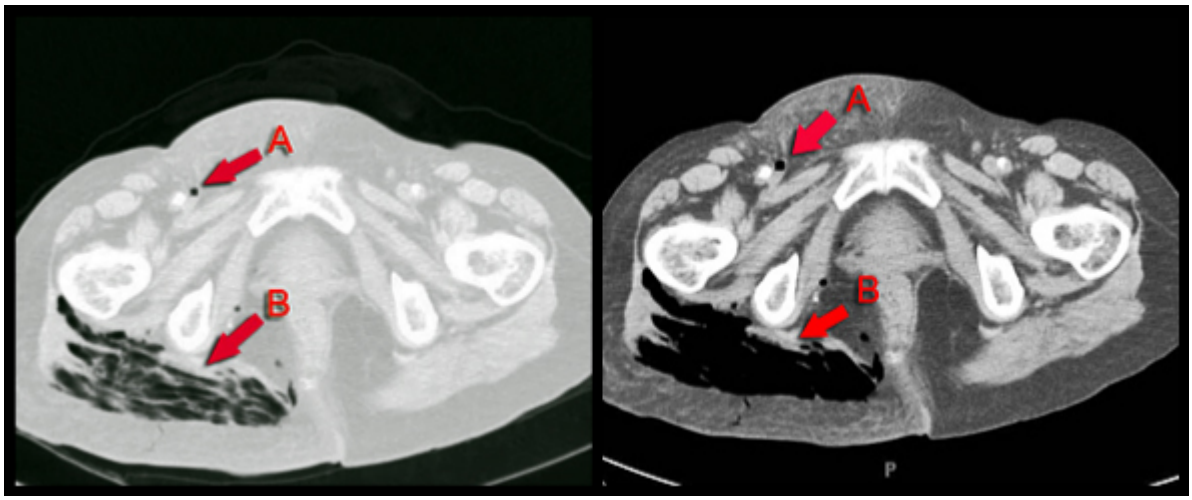


Hematoxylin and eosin-stained biopsy of muscle (x400) from a patient with clostridial gas gangrene shows extensive necrosis.

Courtesy of Stephen Calderwood, MD.

Graphic 62665 Version 2.0

Clostridial myonecrosis computed tomography



Necrotizing fasciitis due to *Clostridium septicum*. Air is demonstrated in the external iliac vein, with air fluid level (Arrow A). Gas in the soft tissue of the buttock is also seen (Arrow B).

Courtesy of William Mann, MD.

Graphic 69941 Version 4.0

Approach to vancomycin dosing for adults with normal kidney function*

Loading dose (for patients with known or suspected severe *Staphylococcus aureus* infection)¶	Load 20 to 35 mg/kg (based on actual body weight, rounded to the nearest 250 mg increment; not to exceed 3000 mg). Within this range, we use a highe dose for critically ill patients; we use a lower dose for patients who are obese and/or are receiving vancomycin via continuous infusion.
Initial maintenance dose and interval	Typically 15 to 20 mg/kg every 8 to 12 hours for most patients (based on actual body weight, rounded to the nearest 250 mg increment). In general, the approach to establishing the vancomycin dose/interval is guided by a nomogram.Δ
Subsequent dose and interval adjustments	Based on AUC-guided (preferred for severe infection)[1] or trough-guided serum concentration monitoring.◇

AUC: area under the 24-hour time-concentration curve.

* Refer to the UpToDate topic on vancomycin dosing for management of patients with abnormal kidney function.

¶ For patients with known or suspected severe *S. aureus* infection, we suggest administration of a loading dose to reduce the likelihood of suboptimal initial vancomycin exposure. Severe *S. aureus* infections include (but are not limited to) bacteremia, endocarditis, osteomyelitis, prosthetic joint infection, pneumonia warranting hospitalization, infection involving the central nervous system, or infection causing critical illness.

Δ If possible, the nomogram should be developed and validated at the institution where it is used to best reflect the regional patient population. Refer to the UpToDate topic on vancomycin dosing for sample nomogram.

◇ Refer to the UpToDate topic on vancomycin dosing for discussion of AUC-guided and trough-guided vancomycin dosing. For patients with nonsevere infection who receive vancomycin for <3 days (in the setting of stable kidney function and absence of other risk factors for altered vancomycin kinetics), vancomycin concentration monitoring is often omitted; the value of such monitoring prior to achieving steady state (usually around treatment day 2 to 3) is uncertain.

Reference:

1. *Rybak MJ, Le J, Lodise TP, et al. Therapeutic Monitoring of Vancomycin for Serious Methicillin-Resistant Staphylococcus Aureus Infections: A Revised Consensus Guideline and Review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm 2020; 77:835.*

Graphic 128911 Version 5.0

Differential diagnosis of necrotizing myositis and fasciitis

Clinical finding	Type I*	Type II*	Gas gangrene	Pyomyositis	Myositis viral/parasiti
Fever	++	++++	+++	++	++
Diffuse pain	+	+	+	+	++++¶
Local pain	++	++++Δ	++++	++	++
Systemic toxicity	++	++++	++++	+	+
Gas in tissue	++	–	++++	–	–
Obvious portal of entry	++++	±◇	++++§	–	–
Diabetes mellitus	++++	±	–	–	–

* Type I and type II refer to the forms of necrotizing fasciitis; spontaneous gangrenous myositis is type II.

¶ Pain with influenza consists of diffuse myalgia; pleurodynia may be associated with severe, localized pain (eg, devil's grip); pain with trichinosis may be severe and localized.

Δ Severe pain is associated with necrotizing fasciitis due to group A streptococcal infection; the pain may not be severe in type I necrotizing fasciitis because it is commonly associated with diabetes with neuropathy.

◇ 50% of patients with necrotizing fasciitis due to group A streptococcal infection do not have an obvious portal of entry.

§ Gas gangrene associated with trauma may be caused by *Clostridium perfringens*, *C. septicum*, or *C. histolyticum*, which always have an obvious portal of entry; in comparison, spontaneous gas gangrene caused by *C. septicum* usually does not have an obvious portal of entry (organisms lodge in tissue as a result of bacteremia originating from a bowel portal of entry).

Graphic 68260 Version 5.0