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159 Gas Gangrene and Other Clostridial Infections

1315 botulism cases were reported from 25 countries, with the most cases in Italy (311 cases), Romania (239 cases), and Poland (202 cases). Foodborne botulism is the most common form of botulism in Europe. Most laboratory-confirmed cases reported from Italy, Romania, and Poland were due to BoNT serotype B. The country of Georgia has a high incidence of botulism (0.9 case per 100,000 persons) relative to rates in the European Union (<0.1/100,000) and the United States (0.01/100,000). From 1980 to 2002, a total of 879 cases of botulism were reported in Georgia; all of them were foodborne, most were associated with home-preserved vegetables, and the majority were due to serotype B. From 1958 to 1983, 986 foodborne botulism outbreaks affecting 4377 individuals were reported from China. Most cases were due to serotype A and were associated with bean products. Botulism in Thailand has been associated with fermented bamboo shoots and fermented soybeans. In 2006, a large foodborne botulism outbreak associated with bamboo shoots occurred in Thailand and affected 209 people who attended a local festival. In South America, Brazil and Argentina have reported several outbreaks of foodborne botulism. For instance, between 2001 and 2008, Brazil reported 18 outbreaks, most of which were associated with meat-based foods such as home-canned meat, homemade pork liver pâté, and commercially canned liver pâté. From 1994 to 2007, Argentina reported 36 outbreaks, most frequently involving home-canned vegetables. Although reports of foodborne botulism in Africa are rare, 5 outbreaks were reported in South Africa between 1959 and 2002, with the majority due to serotype B and associ ated with noncommercial foods. In addition, 1 outbreak of 91 cases was reported in Egypt in 1991 and was due to serotype E associated with a traditional salted fish.

Wound botulism cases have been reported most frequently from the United States, next most frequently from the United Kingdom, and occasionally from Italy, France, and Australia. Clusters of wound botulism are rare, but, according to a report from the European Cen tre for Disease Prevention and Control, 23 cases of wound botulism among people who had injected heroin were reported in Norway and Scotland between December 2014 and February 2015. Other countries that have reported wound botulism cases include Argentina, China, and Ecuador. PART 5 Infectious Diseases Although rarely reported, infant botulism cases have been noted on all continents except Africa. Outside the United States (where there were 2419 cases), Argentina reported the largest number of cases (366) and Australia the next largest number (32) between 1976 and 2006.

Canada, Italy, and Japan also reported a relatively large number of cases (27, 26, and 22, respectively). ■ ■FURTHER READING Centers for Disease Control and Prevention: Botulism in the United States, 1899–1996. Handbook for Epidemiologists, Clinicians, and Laboratory Workers. Atlanta, Centers for Disease Control and Prevention, 1998. Centers for Disease Control and Prevention: National Botulism Surveillance. Available at https://www.cdc.gov/botulism/php/nationalbotulism-surveillance/. Accessed December 19, 2023. Dorner MB et al: A large travel-associated outbreak of iatrogenic botulism in four European countries following intragastric botulinum neurotoxin injections for weight reduction, Türkiye, February to March 2023. Euro Surveill 28:2300203, 2023. European Centre for Disease Prevention and Control: Botulism. Available at www.ecdc.europa.eu/en/botulism. Accessed September 27, 2020. Fleck-Derderian S et al: The epidemiology of foodborne botulism outbreaks: A systematic review. Clin Infect Dis 66:S73, 2017. Koepke R et al: Global occurrence of infant botulism, 1976–2006. Pediatrics 122:e73, 2008. National Center for Home Food Preservation: USDA Complete Guide to Home Canning, 2015 Revision. Available at nchfp.uga.edu/papers/guide/INTRO_HomeCanrev0715.pdf. Accessed March 18, 2024. Peck M et al: Historical perspectives and guidelines for botulinum neurotoxin subtype nomenclature. Toxins (Basel) 9:38, 2017.

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Gas Gangrene and Other Clostridial Infections The genus Clostridium encompasses >60 species that may be com mensals of the gut microflora or may cause a variety of infections in humans and animals through the production of a plethora of pro teinaceous exotoxins. C. tetani and C. botulinum, for example, cause specific clinical disease by elaborating single but highly potent toxins. In contrast, C. perfringens and C. septicum cause aggressive necrotizing infections that are attributable to multiple toxins, including bacterial proteases, phospholipases, and cytotoxins. ETIOLOGIC AGENT Vegetative cells of Clostridium species are pleomorphic, rod-shaped, and arranged singly or in short chains (Fig. 159-1); the cells have rounded or sometimes pointed ends. Although clostridia stain gram-positive in the early stages of growth, they may appear to be gram-negative or gram-variable later in the growth cycle or in infected tissue specimens. Most strains are motile by means of peritrichous flagella; C. septicum swarms on solid media. Nonmotile species include C. perfringens, C. ramosum, and C. innocuum. Most species are obligately anaerobic, although clostridial tolerance to oxygen varies widely; some species (e.g., C. septicum, C. tertium) will grow but will not sporulate in air. Clostridia produce more protein toxins than any other bacterial genus, and more than 25 clostridial toxins lethal to mice have been identified. These proteins include neurotoxins, enterotoxins, cytotoxins, FIGURE 159-1 Scanning electron micrograph of C. perfringens.

collagenases, permeases, necrotizing toxins, lipases, lecithinases, hemo lysins, proteinases, hyaluronidases, DNases, ADP-ribosyltransferases, and neuraminidases. Botulinum and tetanus

neurotoxins are the most potent toxins known, with lethal doses of 0.2–10 ng/kg for humans. Epsilon toxin, a 33-kDa protein produced by C. perfringens types B and D, causes edema and hemorrhage in the brain, heart, spinal cord, and kidneys of animals. It is among the most lethal of the clostridial toxins and is considered a potential agent of bioterrorism (Chap. S4). The genomic sequences of some pathogenic clostridia are now available and are likely to facilitate a comprehensive approach to understanding the virulence factors involved in clostridial pathogenesis. EPIDEMIOLOGY AND TRANSMISSION Clostridium species are widespread in nature, forming endospores that are commonly found in soil, feces, sewage, and marine sediments. The ecology of C. perfringens in soil is greatly influenced by the degree and duration of animal husbandry in a given location and is relevant to the incidence of gas gangrene caused by contamination of wounds with soil. For example, the incidence of clostridial gas gangrene is higher in agricultural regions of Europe than in the Sahara Desert of Africa. Similarly, the incidences of tetanus and food-borne botulism are clearly related to the presence of clostridial spores in soil, water, and many foods. Clostridia are present in large numbers in the indigenous microbiota of the intestinal tract of humans and animals, in the female genital tract, and on the oral mucosa. It should be noted that not all commensal clostridia are toxigenic. Clostridial infections remain a serious public health concern worldwide. In developing nations, food poisoning, necrotizing enterocolitis, and gas gangrene are common because large por tions of the population are poor and have little or no immediate access to health care. These infections remain prevalent in developed coun tries as well. Gas gangrene commonly follows knife or gunshot wounds or vehicular accidents or develops as a complication of surgery or gas trointestinal carcinoma. Severe clostridial infections have emerged as a health threat to injection drug users and to women undergoing child birth or abortion. Historically, clostridial gas gangrene has been the scourge of the battlefield. The global political situation portends another possible scenario involving mass casualties of war or terrorism, with extensive injuries conducive to gas gangrene. Therefore, there is an ongoing need to develop novel strategies to prevent or attenuate the course of clostridial infections in both civilians and military personnel. Vaccination against exotoxins important in pathogenesis would be of great benefit in developing nations and could also be used safely in atrisk populations such as the elderly, patients with diabetes who may require lower-limb surgery due to trauma or poor circulation, and those undergoing intestinal surgery. Moreover, a hyperimmune globu lin would be a valuable tool for prophylaxis in victims of acute TABLE 159-1 Treatment of Clostridial Infections CONDITION ANTIBIOTIC TREATMENT PENICILLIN ALLERGY ADJUNCTIVE TREATMENT/NOTE Wound contamination None — Treatment should be based on clinical signs and symptoms as listed below and not solely on bacteriologic findings. Polymicrobial anaerobic infections involving clostridia (e.g., abdominal wall, gynecologic) Ampicillin (2 g IV q4h) plus Clindamycin (600–900 mg IV q6–8h) plus Ciprofloxacin (400 mg IV q6–8h) Vancomycin (1 g IV q12h) plus Metronidazole (500 mg IV q6h) plus Ciprofloxacin (400 mg IV q6–8h) Clostridial sepsis Penicillin (3–4 mU IV q4–6h) plus Clindamycin (600–900 mg IV q6–8h) Clindamycin alone or Metronidazole (as above) or Vancomycin (as above) Gas gangrene Penicillin G (4 mU IV q4–6h) plus Clindamycin (600–900 mg IV q6–8h) Cefoxitin (2 g IV q6h) plus Clindamycin (600–900 mg IV q6–8h)

traumatic injury or for attenuation of the spread of infection in patients with established gas gangrene.

CLINICAL SYNDROMES Life-threatening clostridial infections range from intoxications (e.g., food poisoning, tetanus) to necrotizing enteritis/colitis, bacteremia, myonecrosis, and toxic shock

syndrome (TSS). Tetanus and botulism are discussed in Chaps. 157 and 158, respectively. Colitis due to C. difficile is discussed in Chap. 139. ■ ■CLOSTRIDIAL WOUND CONTAMINATION Of open traumatic wounds, 30–80% reportedly are contaminated with clostridial species. In the absence of devitalized tissue, the pres ence of clostridia does not necessarily lead to infection. In traumatic injuries, clostridia are isolated with equal frequency from both sup purative and well-healing wounds. Thus, diagnosis and treatment of clostridial infection should be based on clinical signs and symptoms and not solely on bacteriologic findings. ■ ■POLYMICROBIAL INFECTIONS

INVOLVING CLOSTRIDIA Clostridial species may be found in polymicrobial infections also involv ing microbial components of the endogenous flora. In these infections, clostridia often appear in association with non-spore-forming anaerobes and facultative or aerobic organisms. Head and neck infections, conjunc tivitis, brain abscess, sinusitis, otitis, aspiration pneumonia, lung abscess, pleural empyema, cholecystitis, septic arthritis, and bone infections all may involve clostridia. These conditions are often associated with severe local inflammation but may lack the characteristic systemic signs of tox icity and rapid progression seen in other clostridial infections. In addi tion, clostridia are isolated from ~66% of intraabdominal infections in which the mucosal integrity of the bowel or respiratory system has been compromised. In this setting, C. ramosum, C. perfringens, and C. bifer mentans are the most commonly isolated species. Their presence does not invariably lead to a poor outcome. Clostridia have been isolated from suppurative infections of the female genital tract (e.g., ovarian or pelvic abscess) and from diseased gallbladders. Although the most frequently isolated species is C. perfringens, gangrene is not typically observed; however, gas formation in the biliary system can lead to emphysematous cholecystitis, especially in diabetic patients. C. perfringens in association with mixed aerobic and anaerobic microbes can cause aggressive lifethreatening type I necrotizing fasciitis or Fournier’s gangrene. CHAPTER 159 Gas Gangrene and Other Clostridial Infections The treatment of mixed aerobic/anaerobic infection of the abdo men, perineum, or gynecologic organs should be based on Gram staining, culture, and antibiotic sensitivity information. Reasonable empirical treatment consists of ampicillin or ampicillin/sulbactam combined with either clindamycin or metronidazole (Table 159-1). Empirical therapy should be initiated. Therapy should be based on Gram stain and culture results and on sensitivity data when available. Add gram-negative coverage if indicated (see text). Transient bacteremia without signs of systemic toxicity may be clinically insignificant. Emergent surgical exploration and thorough debridement are extremely important. Hyperbaric oxygen therapy may be considered after surgery and antibiotic initiation.

Broader gram-negative coverage may be necessary if the patient has recently been hospitalized or treated with antibiotics. Such coverage can be obtained by substituting ticarcillin/clavulanic acid, piperacillin/

sulbactam, or a carbapenem antibiotic for ampicillin or by adding a fluoroquinolone or an aminoglycoside to the regimen. Empirical treatment should be given for 10–14 days or until the patient’s clinical condition improves.

■ ■ENTERIC CLOSTRIDIAL INFECTIONS C. perfringens type A is one of the most common bacterial causes of food-borne illness in the United States and Canada. The foods typically implicated include improperly cooked meat and meat products (e.g., gravy) in which residual spores germinate and proliferate during slow cooling or insufficient reheating. Illness results from the ingestion of food

containing at least ~108 viable vegetative cells, which sporulate in the alkaline environment of the small intestine, producing C. perfrin gens enterotoxin in the process. The diarrhea that develops within 7–30 h of ingestion of contaminated food is generally mild and self-limiting; however, in the very young, the elderly, and the immunocompromised, symptoms are more severe and occasionally fatal. Enterotoxin-producing C. perfringens has been implicated as an etiologic agent of persistent diarrhea in elderly patients in nursing homes and tertiary-care institu tions and has been considered to play a role in antibiotic-associated diarrhea without pseudomembranous colitis. C. perfringens strains associated with food poisoning possess the gene (cpe) coding for enterotoxin, which acts by forming pores in host cell membranes. C. perfringens strains isolated from nonfood-borne diseases, such as antibiotic-associated and sporadic diar rhea, carry cpe on a plasmid that may be transmitted to other strains. Several methods have been described for the detection of C. perfringens enterotoxin in feces, including cell culture assay (Vero cells), enzymelinked immunosorbent assay, reversed-phase latex agglutination, and polymerase chain reaction (PCR) amplification of cpe. Each method has its advantages and limitations. Interestingly, spores from these strains are particularly resistant to heat, cold, and chemical preserva tives. In addition, the extracellular sialidase produced by C. perfringens facilitates pathogenesis. PART 5 Infectious Diseases Enteritis necroticans (gas gangrene of the bowel) is a fulminating clinical illness characterized by extensive necrosis of the intestinal mucosa and wall. Cases can occur sporadically in adults or as epidemics in people of all ages. Enteritis necroticans is caused by

α toxin– and β toxin–producing strains of C. perfringens type C; β toxin is located on a plasmid and is mainly responsible for pathogenesis. This life-threatening infection causes ischemic necrosis of the jejunum. In Papua New Guinea during the 1960s, enteritis necroticans (known in that locale as pigbel) was found to be the most common cause of death in childhood; it was associated with pig feasts and occurred both spo radically and in outbreaks. Intramuscular immunization against the

β toxin resulted in a decreased incidence of the disease in Papua New Guinea, although the condition remains common. Enteritis necroti cans has also been recognized in the United States, the United Kingdom, Germany (where it is known as darmbrand), and other developed nations; especially affected are adults who are malnourished or who have diabetes, alcoholic liver disease, or neutropenia. Necrotizing enterocolitis, a disease resembling enteritis necroticans but associated with C. perfringens type A, has been found in North America in previously healthy adults. It is also a serious gastrointes tinal disease of low-birth-weight (premature) infants hospitalized in neonatal intensive care units. The etiology and pathogenesis of this disease have remained enigmatic for more than four decades. Pathologic similarities between necrotizing enterocolitis and enteritis necroticans include the pattern of small-bowel necrosis involving the submucosa, mucosa, and muscularis; the presence of gas dissecting the tissue planes; and the degree of inflammation. In contrast to enteritis necroticans, which most commonly involves the jejunum, necrotizing enterocolitis affects the ileum and frequently the ileocecal valve. Both diseases may manifest as intestinal gas cysts, although this feature is more common in necrotizing enterocolitis. The sources of the gas, which contains hydrogen, methane, and carbon dioxide, are probably

the fermentative activities of intestinal bacteria, including clostridia. Epidemiologic data support an important role for C. perfringens or other gas-producing microorganisms (e.g., C. neonatale, certain other clostridia, or Klebsiella species) in the pathogenesis of necrotizing enterocolitis. Patients with suspected clostridial enteric infection should undergo nasogastric suction and receive IV fluids.

Pyrantel is given by mouth, and the bowel is rested by fasting. Benzylpenicillin (1 mU) is given IV every 4 h, and the patient is observed for complications requiring surgery. Patients with mild cases recover without surgical intervention. However, if surgical indications are present (gas in the peritoneal cav ity, absent bowel sounds, rebound tenderness, abdominal rigidity), the mortality rate ranges from 35 to 100%; a fatal outcome is due in part to perforation of the intestine. As pigbel continues to be a common disease in Papua New Guinea, consideration should be given to the use of a C. perfringens type C β toxoid vaccine in local areas. Two doses given 3–4 months apart are preventive. ■ ■CLOSTRIDIAL BACTEREMIA Clostridium species are important causes of bloodstream infections. Molecular epidemiologic studies of anaerobic bacteremia have identi fied C. perfringens and C. tertium as the two most frequently isolated species; these organisms cause up to 79 and 5%, respectively, of clos tridial bacteremias. Occasionally, C. perfringens bacteremia occurs in the absence of an identifiable infection at another site. When associated with myonecrosis, bacteremia has a grave prognosis. C. septicum is also commonly associated with bacteremia. This spe cies is isolated only rarely from the feces of healthy individuals but may be found in the normal appendix. More than 50% of patients whose blood cultures are positive for this organism have some gastrointestinal anomaly (e.g., diverticular disease) or underlying malignancy (e.g., carcinoma of the colon). In addition, a clinically important associa tion of C. septicum bacteremia with neutropenia of any origin—and, more specifically, with neutropenic enterocolitis involving the terminal ileum or cecum—has been observed. Patients with diabetes mellitus, severe atherosclerotic cardiovascular disease, or anaerobic myonecrosis (gas gangrene) also may develop C. septicum bacteremia. C. septicum has been recovered from the bloodstream of cirrhotic patients, as have C. perfringens, C. bifermentans, and other clostridia. Infections of the bloodstream by C. sordellii and C. perfringens have been associated with TSS. Of note, Clostridium sordellii has been recently renamed Paeniclostridium sordellii. However, throughout this text, the authors have used the original nomenclature for this pathogen. Bloodstream infection by C. tertium, either alone or in combination with C. septicum or C. perfringens, can be found in patients with seri ous underlying disease such as malignancy or acute pancreatitis, with or without neutropenic enterocolitis; the frequency has not been sys tematically studied. C. tertium may present special problems in terms of both identification and treatment. This organism may stain gramnegative; is aerotolerant; and is resistant to metronidazole, clindamy cin, and cephalosporins. Other clostridia from the C. clostridioforme group (including C. clostridioforme, C. hathewayi, and C. bolteae) can cause bacteremia. The clinical importance of recognizing clostridial bacteremia—especially that due to C. septicum—and starting appropriate treatment immediately (Table 159-1) cannot be overemphasized. Patients with this condition usually are gravely ill, and infection may metastasize to distant anatomic sites, resulting in spontaneous myonecrosis (see next section). Alternative methods to identify bacteremia-causing clostridial species, such as PCR or other rapid diagnostic tests, are not currently available. Anaerobic blood cultures and Gram’s stain inter pretation remain the best diagnostic tests at this point. ■ ■CLOSTRIDIAL SKIN AND SOFT TISSUE INFECTIONS Histotoxic clostridial species such as C. perfringens, C. histolyticum, C. septicum, C. novyi, and C. sordellii cause aggressive necrotizing infections of the skin and soft tissues. These infections are attributable

in part to the elaboration of bacterial proteases, phospholipases, and cytotoxins. Necrotizing clostridial soft tissue infections are rapidly progressive and are characterized by marked tissue destruction, gas in the tissues, and shock; they frequently end in death. Severe pain, crepitus, brawny induration with rapid progression to skin sloughing, violaceous bullae, and marked

tachycardia are characteristics found in the majority of patients. Clostridial Myonecrosis (Gas Gangrene) • TRAUMATIC GAS GANGRENE C. perfringens myonecrosis (gas gangrene) is one of the most fulminant gram-positive bacterial infections of humans. Even with appropriate antibiotic therapy and management in an intensive care unit, tissue destruction can progress rapidly. Gas gangrene is accompanied by bacteremia, hypotension, and multiorgan failure and is invariably fatal if untreated. Gas gangrene is a true emergency and requires immediate surgical debridement. The development of gas gangrene requires an anaerobic environ ment and contamination of a wound with spores or vegetative organ isms. Devitalized tissue, foreign bodies, and ischemia reduce locally available oxygen levels and favor outgrowth of vegetative cells and spores. Thus, conditions predisposing to traumatic gas gangrene include crush-type injury, laceration of large or medium-sized arter ies, and open fractures of long bones that are contaminated with soil or bits of clothing containing the bacterial spores. Gas gangrene of the abdominal wall and flanks follows penetrating injuries such as knife or gunshot wounds that are sufficient to compromise intestinal integrity, with resultant leakage of the bowel contents into the soft tissues. Prox imity to fecal sources of bacteria is a risk factor for cases following hip surgery, adrenaline injections into the buttocks, or amputation of the leg for ischemic vascular disease. In addition, cutaneous gas gangrene caused by C. perfringens, C. novyi, and C. sordellii has been described in the United States and northern Europe among persons injecting blacktar heroin subcutaneously. The incubation period for traumatic gas gangrene can be as short as 6 h and is usually <4 days. The infection is characterized by the sudden onset of excruciating pain at the affected site and the rapid develop ment of a foul-smelling wound containing a thin serosanguineous discharge and gas bubbles. Brawny edema and induration develop and give way to cutaneous blisters containing bluish to maroon-colored fluid. Such tissue later may become liquefied and slough. The margin between healthy and necrotic tissue often advances several inches per hour despite appropriate antibiotic therapy, and radical amputation remains the single best life-saving intervention. Shock and organ fail ure frequently accompany gas gangrene; when patients become bacte remic, the mortality rate exceeds 50%. Diagnosis of traumatic gas gangrene is not difficult because the infection always begins at the site of significant trauma, is associated with gas in the tissue, and is rapidly progressive. Gram staining of drainage or tissue biopsy is usually definitive, demonstrating large gram-positive (or gram-variable) rods, an absence of inflammatory cells, and widespread soft tissue necrosis. SPONTANEOUS (NONTRAUMATIC) GAS GANGRENE Spontaneous gas gangrene generally occurs via hematogenous seeding of normal muscle with histotoxic clostridia—principally C. perfringens, C. septicum, and C. novyi and occasionally C. tertium—from a gastrointestinal tract portal of entry (as in colonic malignancy, inflammatory bowel disease, diverticulitis, necrotizing enterocolitis, cecitis, or distal ileitis or after gastrointestinal surgery, including colonoscopic polypectomy). These gastrointestinal pathologies permit bacterial access to the bloodstream; consequently, aerotolerant C. septicum can proliferate in normal tis sues. Patients surviving bacteremia or spontaneous gangrene due to C. septicum should undergo aggressive diagnostic studies to rule out gastrointestinal pathology. Additional predisposing host factors include leukemia, lymphopro liferative disorders, cancer chemotherapy, radiation therapy, and AIDS. Cyclic, congenital, or acquired neutropenia also is strongly associ ated with an increased incidence of spontaneous gas gangrene due to C. septicum; in such cases, necrotizing enterocolitis, cecitis, or distal ileitis is common, particularly among children.

CHAPTER 159 FIGURE 159-2 Radiograph of patient with spontaneous gas gangrene due to C. septicum, demonstrating gas in the affected arm and shoulder. The first symptom of spontaneous

gas gangrene may be confusion followed by the abrupt onset of excruciating pain in the absence of trauma. These findings, along with fever, should heighten suspicion of spontaneous gas gangrene. However, because of the lack of an obvious portal of entry, the correct diagnosis is frequently delayed or missed. The infection is characterized by rapid progression of tissue destruction with demonstrable gas in the tissue (Fig. 159-2). Swelling increases, and bullae filled with clear, cloudy, hemorrhagic, or purplish fluid appear. The surrounding skin has a purple hue, which may reflect vascular compromise resulting from the diffusion of bacterial toxins into surrounding tissues. Invasion of healthy tissue rapidly ensues, with quick progression to shock and multiple-organ failure. Mortality rates in this setting range from 67 to 100% among adults; among children, the mortality rate is 59%, with the majority of deaths occurring within 24 h of onset. Gas Gangrene and Other Clostridial Infections PATHOGENESIS OF GAS GANGRENE In traumatic gas gangrene, organ isms are introduced into devitalized tissue. It is important to recognize that for C. perfringens and C. novyi, trauma must be sufficient to inter rupt the blood supply and thereby to establish an optimal anaerobic environment for growth of these species. These conditions are not strictly required for the more aerotolerant species such as C. septicum and C. tertium, which can seed normal tissues from gastrointestinal lesions. Once introduced into an appropriate niche, the organisms proliferate locally and elaborate exotoxins. The major C. perfringens extracellular toxins implicated in gas gangrene are α toxin and θ toxin. A lethal hemolysin that has both phospholipase C and sphingomyelinase activities, α toxin has been implicated as the major virulence factor of C. perfringens: immuniza tion of mice with the C-terminal domain of α toxin provides protection against lethal challenge with C. perfringens, and isogenic α toxin– deficient mutant strains of C. perfringens are not lethal in a murine model of gas gangrene. Recently, a human single chain recombinant antibody against α toxin has been developed having significant preven tative and therapeutic efficacy in mice. It has been shown in experimental models that the severe pain, rapid progression, marked tissue destruction, and absence of neutro phils in C. perfringens gas gangrene are attributable in large part to

Platelet P-selectin gpIIb/IIIa Fibrinogen PSGL-1 CD11b/CD18 Carbohydrates Leukocyte FIGURE 159-3 Schematic illustration of the molecular mechanisms of C. perfringens α toxin–induced platelet/neutrophil aggregates. Homotypic aggregates of platelets (not shown) and heterotypic aggregates of platelets and leukocytes are due to α toxin–induced activation of the platelet fibrinogen receptor gpIIb/IIIa and upregulation of leukocyte CD11b/CD18. Binding of fibrinogen (red) bridges the connection between these adhesion molecules on adjacent cells. An auxiliary role for α toxin–induced upregulation of platelet P-selectin and its binding to leukocyte P-selectin glycoprotein ligand 1 (PSGL-1) or other leukocyte surface carbohydrates also has been demonstrated. α toxin–induced occlusion of blood vessels by heterotypic aggregates of platelets and neutrophils. The formation of these aggregates, which occurs within minutes, is largely mediated by α toxin’s ability to activate the platelet adhesion molecule gpIIb/IIIa (Fig. 159-3); the implication is that platelet glycoprotein inhibitors (e.g., eptifibatide, abciximab) may be therapeutic for maintaining tissue blood flow. PART 5 Infectious Diseases C. perfringens θ toxin (perfringolysin, PFO) is a member of the thiolactivated cytolysin family known as cholesterol-dependent cytolysins, which includes streptolysin O from group A Streptococcus, pneumoly sin from Streptococcus pneumoniae, and several other toxins. Cholesteroldependent cytolysins bind as oligomers to cholesterol in host cell membranes. At high concentrations, these toxins form ring-like pores resulting in cell lysis. At sublytic concentrations, PFO hyperactivates phagocytes and vascular endothelial cells. PFO-mediated activation of the macrophage inflammasome, with production of IL-

1β, has also been reported. Cardiovascular collapse and end-organ failure occur late in the course of C. perfringens gas gangrene and are largely attributable to both direct and indirect effects of α and θ toxins. In experimental models, θ toxin causes markedly reduced systemic vascular resistance but increased car diac output (i.e., “warm shock”), probably via induction of endogenous mediators (e.g., prostacyclin, platelet-activating factor) that cause vasodi lation. This effect is similar to that observed in gram-negative sepsis. In sharp contrast, α toxin directly suppresses myocardial contractility; the consequence is profound hypotension due to a sudden reduction in car diac output. The roles of other endogenous mediators, such as cytokines (e.g., tumor necrosis factor, interleukins 1 and 6) and vasodilators (e.g., bradykinin) have not been fully elucidated. C. septicum produces four main toxins—α toxin (lethal, hemolytic, necrotizing activity), β toxin (DNase), γ toxin (hyaluronidase), and Δ toxin (septicolysin, an oxygen-labile hemolysin)—as well as a protease and a neuraminidase. Unlike the α toxin of C. perfringens, that of C. septicum does not possess phospholipase activity. The mechanisms remain to be fully elucidated, but it is likely that each of these toxins contributes uniquely to C. septicum gas gangrene. TREATMENT Gas Gangrene Patients with suspected gas gangrene (either traumatic or sponta neous) should undergo prompt surgical inspection of the infected

FIGURE 159-4 Histopathology of experimental gas gangrene due to C. perfringens, demonstrating widespread muscle necrosis, a paucity of leukocytes in infected tissues, and accumulation of leukocytes in adjacent vessels (arrows). These features are due to the effects of α and θ toxins on muscle cells, platelets, leukocytes, and endothelial cells. site. Direct examination of a gram-stained smear of the involved tissues is of major importance. Characteristic histologic findings in clostridial gas gangrene include widespread tissue destruction, a paucity of leukocytes in infected tissues in conjunction with an accumulation of leukocytes in adjacent vessels (Fig. 159-4), and the presence of gram-positive rods (with or without spores). Com puted tomography (CT) and magnetic resonance imaging (MRI) are invaluable for determining whether the infection is localized or is spreading along fascial planes, and needle aspiration or punch biopsy may provide an etiologic diagnosis in at least 20% of cases. However, these techniques should not replace surgical exploration, Gram’s staining, and histopathologic examination. When spontane ous gas gangrene is suspected, blood should be cultured since bac teremia usually precedes cutaneous manifestations by several hours. For patients with evidence of clostridial gas gangrene, thor ough emergent surgical debridement is of extreme importance. All devitalized tissue should be widely resected back to healthy via ble muscle and skin so as to remove conditions that allow anaerobic organisms to continue proliferating. Closure of traumatic wounds or compound fractures should be delayed for 5–6 days until it is certain that these sites are free of infection. Antibiotic treatment of traumatic or spontaneous gas gangrene (Table 159-1) consists of the administration of penicillin and clindamycin for 10–14 days. Penicillin is recommended on the basis of in vitro sensitivity data; clindamycin is recommended because of its superior efficacy over penicillin in animal models of C. perfrin gens gas gangrene and in some clinical reports. Controlled clinical trials comparing the efficacy of these agents in humans have not been performed. In the penicillin-allergic patient, clindamycin may be used alone. The superior efficacy of clindamycin is probably due to its ability to inhibit bacterial protein toxin production, its insensitivity to the size of the bacterial load or the stage of bacterial growth, and its ability to modulate the host immune response. Although C. perfringens remains largely susceptible to first-line antibiotics, antibiotic resistance has been reported. Case reports from the United Kingdom and from Spain found clindamycinresistant C. perfringens in cellulitis and in a spontaneous abscess, respectively. Larger studies from Canada

and Taiwan also showed increasing resistance to clindamycin among bloodstream isolates. In 2014, Marchand-Austin et al. published a 2-year prospective Canadian study that examined antimicrobial susceptibility of anaer obic bacteria isolated from blood, body fluids, and abscesses. Of 1412 isolates submitted for susceptibility testing, 68 were C. per fringens. Of these, all were universally susceptible to penicillin, but 3.8% were clindamycin-resistant. Notably, for Clostridium species other than C. perfringens (n = 289), 14.2% were penicillin-resistant

and 21.6% clindamycin-resistant. A more recent study from Iran found that 21.2% of C. perfringens isolates were resistant to penicil lin. Lastly, a 2019 study from Hungary found resistance to penicillin (2.6%) and clindamycin (3.8%) among C. perfringens isolates (n = 313) from tissues with gas gangrene. Among the non-perfringens gas gangrene isolates (n = 59), higher resistance to penicillin and clindamycin was observed (6.8% and 8.5%, respectively). These findings, though not universal, highlight the importance of good anaerobic microbiology susceptibility testing to provide up-to-date information to guide optimal clinical management decisions for clostridial infections. C. tertium is resistant to penicillin, cephalosporins, and clindamy cin. Appropriate antibiotic therapy for C. tertium infection is vanco mycin (1 g every 12 h IV) or metronidazole (500 mg every 8 h IV). The value of adjunctive treatment with hyperbaric oxygen (HBO) for gas gangrene remains controversial. Basic science studies sug gest that HBO can inhibit the growth of C. perfringens but not that of the more aerotolerant C. septicum. In vitro, blood and macerated muscle inhibit the bactericidal potential of HBO. Numerous stud ies in animals demonstrate little efficacy of HBO alone, whereas antibiotics alone—especially those that inhibit bacterial protein synthesis—confer marked benefits. Addition of HBO to the thera peutic regimen provides some additional benefit, but only if surgery and antibiotic administration precede HBO treatment. In conclusion, gas gangrene is a rapidly progressive infection whose outcome depends on prompt recognition, emergent surgery, and timely administration of antibiotics that inhibit toxin produc tion. Gas gangrene associated with bacteremia probably represents a later stage of illness and is associated with the worst outcomes. Emergent surgical debridement is crucial to ensure survival, and ancillary procedures (e.g., CT or MRI) or transport to HBO units should not delay this intervention. Some trauma centers associ ated with HBO units may have special expertise in managing these aggressive infections, but proximity and speed of transfer must be carefully weighed against the need for haste. PROGNOSIS OF GAS GANGRENE The prognosis for patients with gas gangrene is more favorable when the infection involves an extremity rather than the trunk or visceral organs, since debridement of the latter sites is more difficult. Gas gangrene is most likely to progress to shock and death in patients with associated bacteremia and intravascular hemolysis. Mortality rates are highest for patients in shock at the time of diagnosis. Mortality rates are relatively high among patients with spontaneous gas gangrene, especially that due to C. septicum. Survivors of gas gangrene may undergo multiple debridements and face long periods of hospitalization and rehabilitation. PREVENTION OF GAS GANGRENE Initial aggressive debridement of devitalized tissue can reduce the risk of gas gangrene in contaminated deep wounds. Interventions to be avoided include prolonged applica tion of tourniquets and surgical closure of traumatic wounds; patients with compound fractures are at significant risk for gas gangrene if the wound is closed surgically. Vaccination against α toxin is protective in experimental animal models of C. perfringens gas gangrene but has not been investigated in humans. In addition, as mentioned above, a hyper immune globulin would represent a significant advance for prophylaxis in victims of acute traumatic injury or for attenuation of the spread of infection in patients with established gas gangrene. Toxic Shock Syndrome Clostridial infection of the endometrium, particularly that due to C. sordellii, can develop

after gynecologic procedures, childbirth, or abortion (spontaneous or elective, surgical, or medical) and, once established, proceeds rapidly to TSS and death. Systemic manifestations, including edema, effusions, profound leu kocytosis, and hemoconcentration, are followed by the rapid onset of hypotension and multiple-organ failure. Elevation of the hematocrit to 75–80% and leukocytosis of 50,000–200,000 cells/μL, with a left shift, are characteristic of C. sordellii infection. Pain may not be a prominent feature, and fever is typically absent. In one series, 18% of 45 cases of

C. sordellii infection were associated with normal childbirth, 11% with medically induced abortion, and 0.4% with spontaneous abortion; the case-fatality rate was 100% in these groups. Of the infections in this series that were not related to gynecologic procedures or childbirth, 22% occurred in injection drug users, and 50% of these patients died. Other infections followed trauma or surgery (42%), mostly in healthy persons, and 53% of these patients died. Overall, the mortality rate was 69% (31 of 45 cases). Of patients who succumbed, 85% died within 2–6 days after infection onset or following procedures. Rapidly fatal spontaneous C. bifermentans necrotizing endometritis with toxic shock, leukemoid reaction, and capillary leak has also been described.

Early diagnosis of C. sordellii infections often proves difficult for several reasons. First, the prevalence of these infections is low. Sec ond, the initial symptoms are nonspecific and frankly misleading. Early in the course, the illness resembles any number of infectious diseases, including viral syndromes. Given these vague symptoms and an absence of fever, physicians usually do not aggressively pursue additional diagnostic tests. The absence of local evidence of infection and the lack of fever make early diagnosis of C. sordellii infection par ticularly problematic in patients who develop deep-seated infection following childbirth, therapeutic abortion, gastrointestinal surgery, or trauma. Such patients are frequently evaluated for pulmonary embo lization, gastrointestinal bleeding, pyelonephritis, or cholecystitis. Unfortunately, such delays in diagnosis increase the risk of death, and as in most necrotizing soft tissue infections, patients are hypotensive with evidence of organ dysfunction by the time local signs and symp toms become apparent. In contrast, infection is more readily suspected in injection drug users presenting with local swelling, pain, and redness at injection sites; early recognition probably contributes to the lower mortality rates in this group. CHAPTER 159 Physicians should suspect C. sordellii infection in patients who pres ent within 2–7 days after injury, surgery, drug injection, childbirth, or abortion and who report pain, nausea, vomiting, and diarrhea but are afebrile. There is little information regarding appropriate treatment for C. sordellii infections. In fact, the interval between onset of symptoms and death is often so short that there is little time to initiate empirical antimicrobial therapy. Indeed, anaerobic cultures of blood and wound aspirates are time-consuming, and many hospital laboratories do not routinely perform antimicrobial sensitivity testing on anaerobes. Anti biotic susceptibility data from older studies suggest that C. sordellii, like most clostridia, is susceptible to β-lactam antibiotics, clindamycin, tetracycline, and chloramphenicol but is resistant to aminoglycosides and sulfonamides. Antibiotics that suppress toxin synthesis (e.g., clindamycin) may possibly prove useful as therapeutic adjuncts since they are effective in necrotizing infections due to other toxin-produc ing gram-positive organisms. With the adoption of restrictive legisla tion that reduces or prohibits access to medically supervised abortions, the incidence of these deadly clostridial infections could increase as patients undergo unsafe pregnancy termination. Gas Gangrene and Other Clostridial Infections Other Clostridial Skin and Soft-Tissue Infections Crepitant cellulitis (also called anaerobic cellulitis) occurs principally in diabetic patients and characteristically involves subcutaneous tissues or retro peritoneal tissues, whereas the muscle and fascia are not involved. This infection can progress to fulminant systemic disease. Cases of C. histolyticum infection with

cellulitis, abscess forma tion, or endocarditis have also been documented in injection drug users. Endophthalmitis due to C. sordellii or C. perfringens has been described. C. ramosum is also isolated frequently from clinical speci mens, including blood and both intraabdominal and soft tissues. This species may be resistant to clindamycin and multiple cephalosporins. ■ ■FURTHER READING Aldape MJ et al: Clostridium sordellii infection: Epidemiology, clinical findings, and current perspectives on diagnosis and treatment. Clin Infect Dis 43:1436, 2006. Aronoff DM et al: Infections caused by Clostridium perfringens and Paeniclostridium sordellii after unsafe abortion. Lancet Infect Dis 23:e48, 2023. Erratum in: Lancet Infect Dis 22:e310, 2022.

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