Review

Gas Gangrene in Type 2 Diabetes: A Systematic Review of Clinical Challenges and Microbial Etiology

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Gas Gangrene in Type 2 Diabetes: A Systematic Review of Clinical Challenges and Microbial Etiology

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Abstract

Clostridial myonecrosis infection with a swift onset of progression results in a high mortality rate. The main pathogen of the issue is *Clostridium perfringens*. The diabetic patients are prone to showing higher susceptibility to developing foot ulcers due to several reasons, such as vascular insufficiency, neuropathy, and impaired wound healing. Furthermore, diabetics suffer from systemic complications like sepsis and multi-organ failure. Advanced necrosis of tissue leads to limb amputation, with the lower limb being amputated more than the upper extremities. The treatment process challenges include: hyperglycemia, which complicates management; risks of reinfection; and slower healing. Early detection is crucial, as surgical removal of damaged tissue combined with broad-spectrum antibiotics remains an important part of treatment. Patients who experienced hyperbaric oxygen therapy (HBOT) and negative pressure wound therapy (NPWT) are more likely to experience better survival outcomes, as these procedures result in vascular repair, tissue oxygenation, decreased risk of reentrance of bacteria, and lower rates of amputation. This is a retrospective review of both historical and recent literature in clinical, microbiological, and treatment aspects of gas gangrene developed in the context of diabetes.

Keywords: gas gangrene (GG); diabetic mellitus (DM); hyperbaric oxygen therapy (HBOT); negative pressure wound therapy (NPWT); Diabetic foot (DF); C. perfringens-related sudden death (CPRSD)

Introduction

Gas gangrene, also known as clostridial myonecrosis, continues to be a medical emergency, rapidly advancing necrotizing infection. This medical issue is predominantly caused by *Clostridium perfringens*: a toxin-producing, anaerobic, and spore-forming bacterium commonly found in the soil and human intestine (Paquier et al., 2021). Patients, who are in immunocompromised condition such as in diabetic mellitus, have mortality rate of 67% or higher according to Buboltz and Murphy-Lavoie (2023). They also found alpha toxin as the most lethal among other toxicants of clostridium perfringens. The most common location of the infection is mainly the forefoot, which has better prognosis of the treatment by avoiding amputation, compared to midfoot and hindfoot (Aragón-Sánchez et al., 2015).

Immunosuppressed patients, those with uncontrolled diabetic mellitus or receiving chemotherapy, are more vulnerable to develop spontaneous gas gangrene (GG) due to rapid spread of bacteria (Hussain et al., 2024). Factors that cause GG in diabetic patients include local tissue hypoxia caused by injury or inadequate blood flow. Among clostridium species, *C. perfringens* and *histolyticum* are mostly related to post-traumatic infections, while *C. septicum* is the primary cause as spontaneous GG associated with gastrointestinal malignancies like bowel cancer. If the partial pressure of oxygen is below 30 mm Hg, the chances of growing clostridial organisms increase.

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Patients might acquire infection with slow or rapid development over weeks or hours, depending on the partial pressure of oxygen and the quantity of organisms inhabiting.

Buboltz and Murphy-Lavoie (2023) also discovered that intensity of pain for advanced infection is inversely related to degree of damaged nerves. The major threat in diabetic foot and ulcer formation is the loss of sensory perception caused by peripheral nerve damage, which usually serves as the initial expansion trigger. Neuropathy is prominent in about 60% of diabetic patients and its various malfunctions divide into: sensory, motor, and autonomic categories (Pitocco et al., 2019). As a result of decreased sensation, injuries to lower extremities often remain hidden, which further deteriorates the condition. Consequently, sensory nerves are damaged by repetitive plantar pressure and shear forces caused by walking and weight bearing that affect the injured area. Foot deformities, caused by motor neuropathy and lack of muscular balance, form conditions that are more prone to trauma like: foot drop, hammerhead toes, and equinus deformities (Pitocco et al., 2019).

About 60 % of non-trauma related amputations of lower limb belong to Diabetic patients (Pitocco et al., 2019). Thus immunodeficient patients are at more risk. Treatment of GG in diabetic patients is a medical emergency and requires immediate approach to reduce mortality. Facing difficulties like sepsis, failure of multiple organs, and death prioritize the significance of proactive and thorough oversight. Prognosis relies on initial diagnosis and treatment. Clinical presentations of infected wounds include: progressive tissue necrosis and production of gas (Hussain et al., 2024). They also found that general toxic effects include: fever, tachycardia, hypotension, shock, and tachypnea (Pitocco et al., 2019). According to Buboltz and Murphy-Lavoie (2023), a subdermal inflammation process occurs at the site because of the profound nature of the wound and its ability to reach deeper tissues.

The categorisation of diabetic foot infections depends on the description of ulcer characteristics such as: size, depth, appearance, and location. Necrotic, foul smelling, or gangrenous wounds require antianaerobic antibiotics (Pitocco et al., 2019). Initial treatment should start with empiric treatment while including taking cultures. The comprehensive coverage includes: vancomycin, tazobactam, carbapenem, or ceftriaxone with metronidazole. Clindamycin is strongly advised by Buboltz and Murphy-Lavoie (2023) because it destroys the clostridial exotoxins and inhibits the effects of toxins. Due to bacteriostatic abilities of clindamycin, it is recommended to use with secondary antimicrobials like penicillin.

The hyperbaric oxygen therapy (HBOT) is used to improve tissue oxygenation and decrease bacterial growth. Introduction of oxygen, which is at increased atmospheric pressure to hypoxic tissue, inhibits the growth of anaerobic bacteria like *Clostridium* species. HBOT also assists in tissue healing by reducing edema and inflammation, stimulating enhanced angiogenesis and fibroblast activity (Hussain et al., 2024). If there is no infection, the majority of patients need further wound care with: negative pressure wound therapy, regenerative medicine, and plastic procedures like skin grafting and tissue transferring (Buboltz and Murphy-Lavoie 2023). Patients who received HBOT during surgery represented a better condition (Cooney & Cooney, 2011). The cases that involve: advanced bone destruction seen in x-ray, visible bone beneath the skin, damage in soft tissue envelope, and constantly spreading gangrene or soft tissue infection, require special surgery (Aragón-Sánchez et al., 2015).

The complications with treatment can occur due to several reasons: loss of foot sensation because of impaired vision of a patient, neuropathy, misjudgment by a doctor, and delay in recognition of pathogenic organism, which might require the initiation of empirical antibiotic therapy (Pitocco et al., 2019). Another arising obstacle is the reported antibiotic resistance: granted *C. perfringens* is defenseless against first-line antibiotics, other *C. perfringens* show 14.2% and 21.6% resistance to penicillin and clindamycin, respectively (Stevens, Bryant, & Goldstein, 2021).

This review aims to conduct a comprehensive examination of the microbiological factors and evaluate clinical manifestations of clostridial myonecrosis in individuals with diabetes. Given that diabetic patients are particularly susceptible to severe soft tissue infections due to compromised immunity and vascular complications, the objective of this research is to identify infection patterns,

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toxin-related virulence, and common clinical outcomes associated with *C. perfringens.* Emphasis is placed on early diagnosis which allows for the prevention of fatal outcomes by reducing mortality. Relevant data from previous studies about clostridial myonecrosis were obtained from the World Health Organisation.

Etiology

Clostridium perfringens was first discovered in 1891 by William Welch during the autopsy of a 38-year-old man who was diagnosed with pulmonary tuberculosis, military tuberculosis, and a large saccular aneurysm of the ascending aorta with rupture in two places in the anterior chest wall. He discovered that veins and arteries had no indication of incisions but presented with contained gas emboli. The bubbles were present in various organs like the spleen, heart, kidneys, and liver. Microscopic evaluation revealed that bacilli presented as about 3 to 5 μm in length with capsules in pairs, with short chains. A new pathogen was discovered and initially named Bacillus aerogenes capsulatus, but the capsules were not present in all microorganisms. Subsequently, it was called with various terminologies such as: *Bacillus welchii, Bacillus pneumathaemia, Bacillus sanguinis aerogenes, Bacillus aerogenes, Bacillus aerogenes cadaveris, Bacillus phlegmonosus emphysematosus, and Bacillus perfringens* (Grenda et al. 2023).

Regardless of historical appellations, the widespread terminology that is used now is *Clostridium perfringens*. The name *Clostridium*, which was Latinised into Clostridium, originates from the Greek word kloster, which means spindle-shaped. At the same time, the term *perfringens* derives from Latin perfringere, which identifies 'to break' due to its capacity to generate significant volumes of gas, which destroys surfaces of agar-based culture media (Grenda et al. 2023).

In addition, through the use of advanced technology such as next-generation sequencing (NGS), researchers discovered *C. perfringens* in the mummified digestive tract of 5000-year-old Ötzi, also known as 'Tyrolean Iceman', in an alpine glacier in 1991 (Lugli et al., 2017). Life-threatening conditions such as septic wound infections that cause gas gangrene, food-borne illnesses such as enteritis/enterocolitis, and enterotoxemia in animals are caused by a broad-spectrum pathogen - *Clostridium perfringens*. The *C. perfringens* is a gram-positive, spore-forming bacterium; it is classified as an anaerobic organism because of its intolerance to air during cultivation. Compared with other anaerobes, it is more resistant to killing by oxygen (Mehdizadeh Gohari et al., 2021).

The presence of IV pili instead of flagella contributes to surface-associated locomotion, formation of bioform, and adhesion. A comprehensive comparative study was performed of 56 *C. perfringens* species. The results indicated that they consist of (A-G) toxinotypes, which also form from a single circular chromosome. This chromosome involves 11667 genes, the majority of them being accessory (87.4%) and only 12.6% belonging to core genes (Mehdizadeh Gohari et al., 2021).

The crucial form of transmission is spores of *C. perfringens*. They are highly resilient to extreme environments such as high temperatures, the presence of oxygen, or low nutrient levels. These characteristics enable its persistence across diverse environmental niches, including soil, faeces, sewage, food, and the intestinal tract of humans and animals. Significantly resistant *C. perfringens* is considered the second leading responsible pathogen in foodborne bacterial disease in the United States (causing one million illnesses yearly) and in fourth place in Europe. The pathogens' ability to produce various toxins, such as alpha-toxin (CPA, cpa/plc gene), beta-toxin (CPB, cpb gene), epsilon-toxin (ETX,etx gene), and iota-toxin (ITX, iap, and ibp binary genes), is considered the main factor for its organism effects (Camargo et al. 2024).

The food poisoning from *C. perfringens* is historically referred to as Darmbrand in post-World War II Germany, and Pigbell in Papua New Guinea during the 1960s. The malnourished people are the predominant targets of the disease. Foodborne transmission demonstrated a significant occurrence in Papua New Guinea, where children patients suffered from malnutrition and had low trypsin due to their nutrient-deficient diet: extremely large consumption of sweet potatoes that are rich in a protein trypsin inhibitor prevented the breakdown of the disease. Their symptoms included swollen abdomen, "dilated thickened bowel loops with segmental necrosis," and pain (Yao and

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Annamaraju, 2023). Those children were more vulnerable to *C. perfringens*, as they were exposed to undercooked meat, with pork being the main source of meat products.

However, impaired nutritional condition is not the only cause of *C. perfringens* because cases of individuals with diabetes and pancreatic diseases were also noted (Yao and Annamaraju, 2023). Microbiological analysis is essential to determine the responsible microorganism, especially when bacterial colonization leads to wound-developed signs of infection. The reasons: having compromised barriers and reduced immunological defense compared to intact skin in diabetic foot, allow entrance for pathogenic microorganisms (Pitocco et al., 2019).

In cases of GG, the gas is an important step in diagnosis, due to its ability to produce gases like hydrogen and carbon by fermentation of carbohydrates (Hussain et al., 2024). In the majority (70%) of cases of non-diabetic gas gangrene formation, the primary cause is trauma; other underlying conditions include: bowel and biliary tract surgery, intramuscular injection, retained placenta, and intrauterine fatal death. Approximately 80% of infections occur due to *Clostridium perfringens*, an advanced trauma penetrating tissue (Leiblein, M. et al., 2020). A profound tissue-invasive infection, which impairs vascular perfusion, creates an anaerobic condition that is perfect for the initiation of spore germination and subsequent bacterial replication (Stevens, Bryant, & Goldstein, 2021). Other pathogenic microorganisms include: *Clostridium septicum, Clostridium novyi, Clostridium histolyticum, and Clostridium sordelli*; the latter of which is mostly widespread in gynecology field-related infections (Leiblein, M. et al., 2020). GG that occurs spontaneously is caused by *C. septicum* and is more common in patients with portal hypertension in the digestive system. The mechanism is understood as there is an underlying defect in bowel mucosa, due to growing tumor, radiation, chemotherapy, and surgery. In comparison, *C. septicum* is capable of initiating infection in the absence of tissue damage, and it typically affects devitalized tissue because *C. septicum* exhibits greater aerotolerance compared to *C. perfringens* (Lugli et al., 2017). The *Clostridium septicum* primarily affects tissues that were not affected by external trauma and can cause infections that are spontaneous in immunocompromised individuals, or those with underlying conditions such as colorectal cancer, leukemia, and diabetes mellitus (Hussain et al., 2024).

Epidemiology

Diabetic patients are particularly vulnerable to *C. perfringens* due to impaired wound healing and compromised angiogenesis. Angiogenesis is a vital process in wound healing, diabetic complications, such as skin ulceration, and diabetic foot ulcer (DFU). The fibroblasts are essential in angiogenesis by regulating endothelial cells. Different kinds of factors that regulate angiogenesis, such as "endothelial growth factor (VEGF) by Fukumura et al. (1998) and platelet-derived growth factor (PDGF) by Antoniades et al. (1991)", for stimulating proliferation, formation of a tube of endothelial cells (Huang et al. 2020). Microvascular dysfunction leads to: thickening of the basement membrane, disruption of nutrient transport, reduced oxygen availability in tissues, and impaired microvascular perfusion (Pitocco et al. 2019).

The majority of studies prove that high levels of glucose in diabetics are the primary reason for impaired angiogenesis and delay in wound healing. The in vivo research reveals that elevated glucose levels cause loss of integrity and greater predisposition to undergo apoptosis (Huang et al., 2020).

The immunocompromised patient with a deep penetrating wound into muscle is more vulnerable to contracting an infection than a patient with a strong immune system and healthy diet. The majority of open surface-level lesions have low chances of acquiring an infection, notably if wound hygiene and dressing protocols are adequately followed, in comparison to "deeper penetrating wounds or wounds with crush injury and tissue ischemia" (Buboltz and Murphy-Lavoie 2023). The immunocompromised patients, such as diabetics or those with angiopathy, are considered a risk group because of increased infection progression and should seek medical care without delay for cellulitis (Yao & Annamaraju, 2023).

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The classic form of chronic non-healing wound is diabetic foot ulcer (DFU), which leads to infections of soft tissue and osteomyelitis (Cooney & Cooney, 2011). DFUs are a combination of tissue neuropathy, peripheral vascular diseases, deformities of the foot, and infection. The patients with DFU have a considerable escalation in health complications and fatality risks. The infection of the lower limbs is common and can present severe complications. The factor that leads to amputation is when a significant proportion of foot ulcers progress to infection. In acute DFU cases, the late detection of the responsible microorganism usually results in a delay in the use of broad-spectrum antibiotic therapy (Pitocco et al. 2019). The historical evidence of amputations dates back to ancient Egyptian mummies; the foot ulcers were presented in diabetic patients, the mummies presented with prosthetic toes (Pryce, T. D. 1887).

C. perfringens transmits via the fecal–oral pathway, typically through the consumption of polluted food or water. Its spores are highly resilient, surviving harsh conditions—from the acidic environment of the stomach to the anoxic setting of the bowel—where they can germinate and cause infection (Hussain et al., 2024). The majority of gastrointestinal illnesses are caused by contaminated food and other non-food-related sources from *C. perfringens* due to inadequately heated meat products and domestic fowl. Consequently, informing patients about the importance of adherence to rigorous food safety protocols is crucial in preventing and controlling the transmission of disease (Yao & Annamaraju, 2023).

The *C. perfringens* is not only causative of various life-threatening conditions, but also due to the fulminant progression of the disease, sudden death may ensue prior to the establishment of a definitive diagnosis. The C. perfringens-related sudden death (CPRSD), caused by massive intravascular hemolysis (MIH), usually occurs as a sepsis complication and presents with severe anemia, acute renal failure, and disseminated intravascular coagulation (Simon TG et al. 2014).

The MIH is frequently identified in case reports involving post-abortion and postpartum infections, and gas gangrene. The adequate medical approach reduces the cases of these entities. However, advancements in and the intensification of therapeutic approaches for malignant diseases have led to a heightened incidence of severe infections, notably *Clostridial septicemia* (Gutiérrez et al., 1995). Currently, MIH manifests in immunodeficient patients, such as those with diabetes, and those with "malignant neoplasms, especially those with colon cancers and hematological malignancies" (Chinen K. 2020).

The sudden death can be unrelated to MIH and can be caused in the presence or absence of GG. The process occurs via various pathogenic pathways: "acute renal failure, hyperkalemia, disseminated intravascular coagulation (DIC), pulmonary edema, pulmonary hemorrhage, and hemodynamic collapse (shock)". The MIH-causing CPRSD could also happen due to the typical lesions responsible for massive intravascular hemolysis; rare but notable infectious sources have been identified, including "acute tonsillitis, necrotizing enterocolitis, necrotizing pneumonia, and empyema" (Chinen K. 2020).

Moreover, non-malignant diseases such as panenteritis and intestinal arteriovenous malformation (vascular ectasia), and MIH which is secondary to *C. perfringens*. The clinical procedures of digestive and biliary tracts and such as "cholecystectomy, endoscopic retrograde cholangiopancreatography, and transhepatic arterial chemoembolization" may additionally contribute to *C. perfringens*–associated MIH (Chinen K. 2020).

Clinical Description

The GG is categorized into three groups: posttraumatic, postoperative, and spontaneous, each having unique clinical characteristics. The traumatic GG presents with three sequential pathological phases. Phase 1, includes tissue ischemia, resulting in oxidation-reduction potential, and promotes the initiation of germination of pathogens and clostridial spores. Phase 2, incorporates the proliferation of bacteria and the creation of a permissive microenvironment for toxin production. The toxin regulation in *C. perfringens* occurs through a canonical two-component regulatory system, VirSR, in conjunction with a quorum-sensing mechanism analogous to an accessory gene regulator,

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which orchestrates the expression of virulence determinants. Phase 3, consists of damage to tissue on cellular level resulting in necrosis, systemic toxemia, and overt clinical manifestations from toxin exposure (Serafio-Gómez et al. 2023).

The five factors, including perfusion (blood supply), extent (area), depth, infection, and sensation (neuropathy) of the wound, constitute PEDIS guidelines. The PEDIS is the classification system developed by the International Working Group on the Diabetic Foot. The Infectious Diseases Society of America guidelines divide foot ulcers according to the spread of infection from uninfected, to mild cases involving only superficial layers, to moderate forms with deeper tissue involvement, and finally to severe cases presenting with systemic signs (Pitocco et al., 2019).

The medical diagnostic classification system of foot infection in diabetics is typically identified as neuropathic, ischemic, or neuroischemic, determined by the type and impact of complications such as neuropathy of the lower limb and vascular disease, which are considered contributing factors to ulcer development (Paquier et al., 2021).

The traumatic GG is the most ubiquitous form and commonly manifests after injuries that compromise tissue integrity and permit the entry of *C. perfringens* spores into subfascial or muscular planes. The injuries, such as crushing forces, exposed fractures, or perforating soft tissue wounds, are frequently sustained during high-impact events, including motor vehicle collisions or industrial-related traumatic incidents. The traumatic GG is an advanced infection characterized by rapid clinical deterioration, with *C. perfringens* being the main causative pathogen for over 80% of instances. Other Clostridium species: *Clostridium septicum (CS), Clostridium novyi (CN)* type A, and *Clostridium histolyticum* are able to cause pathogenic reactions, though less frequently. The process of bacterial proliferation occurs because CP spores enter into necrotic tissue, the anaerobic environment enhances spores to grow and secrete toxins (Hussain et al., 2024).

The *C. perfringens* can also transmit via blood in the absence of substantial tissue destruction, in many cases related to gastrointestinal diseases like colon cancer and colonic diverticulitis. The patients suffering from conditions such as leukemia, neutropenia, and diabetes mellitus are more prone to developing pathogenic infections. The *C. perfringens* likely enters via gastrointestinal (GI) ulcer and bowel perforation, sometimes causing acute multifocal myonecrosis or profound deep tissue damage (Azimirad et al. 2019)

Effective information gathering during the medical history is essential in further clinical evaluation. Any recent physical injury, operative treatment, or invasive diagnostic procedures in an area of interest may help establish the link between bacterial contamination and GG manifestation. The history provides comprehensive insight into the evaluation of probable bacterial transmission pathways. The clinical hallmarks of GG include: pronounced pain, significant swelling, gas-filled vesicles (bullae), tenderness upon palpation, subcutaneous crepitus, fetid odor, and visible tissue necrosis, which are pivotal for early recognition and diagnosis. Sudden emergence and rapid escalation of systemic clinical symptoms like fever and tachycardia indicate a potential diagnosis of GG (Hussain et al., 2024).

The gas production caused by the fermentation of glucose contributes to rapid infection propagation by dissecting through fascial and subcutaneous compartments. Gas formation in wound tissue is not a solitary indicator of *C. perfringens* infection because other aerobic gram-negative bacteria, such as "*Escherichia coli, Proteus, Pseudomonas aeruginosa,* and *Klebsiella pneumoniae*" show the capacity to produce gas. The absence of a distinct diagnostic indicator that ensures *C. perfringens* pathogenic invasion underscores the importance of recognizing early clinical signs in conjunction with laboratory and radiologic assessments (Hussain et al., 2024).

The DFU is frequently the outcome of diabetic foot infection. These wounds develop with disruption of the skin barrier, commonly in affected areas of trauma, both mechanical and thermal, and ulceration. The inflammatory response occurs because foreign bacteria colonize and proliferate in the host tissue. This initiates a cascade culminating in tissue destruction. The diabetic foot infection is described as the infectious involvement of connective and bone tissue located below the malleoli in patients with diabetes. Diabetics with conditions such as peripheral neuropathy, vascular

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dysfunction, immune system impairment, and altered foot biomechanics are prone to developing foot infection (Pitocco et al. 2019).

Periosteum represents the initial anatomical barrier exposed to pathogen infiltration, resulting in periostitis. Thereafter, if infection reaches cortical and medullary bones, it causes osteitis and osteomyelitis, respectively (Aragón-Sánchez et al., 2015). Conditions such as ulcers with a size exceeding 60 mm^2, chronic purulent discharge through a sinus tract, markedly elevated erythrocyte sedimentation rate (>70 mm/h), or the characteristic swelling known as "sausage toe" may serve as diagnostic indicators that correlate with the potential presence of underlying osteomyelitis. The baseline radiographic modality is an affordable method for osteomyelitis diagnosis (Pitocco et al., 2019).

The forefoot osteomyelitis predominantly affects the phalanges and proximal segments of the metatarsals. The anatomy of the tip of the distal phalanx is located in the forefoot, where there is an absence of joints and tendons. Situated between the dermis and the periosteal membrane, the subcutaneous tissue acts as an intermediate layer because the ulcers of this layer easily reach the bone. Tendons located on the basal surface of the hallux include the flexor hallucis longus (plantar) and extensor hallucis longus (dorsal). Flexor digitorum longus (plantar) and extensor digitorum longus and brevis are terminated on the proximal surface of the distal phalanges of the lateral toes. It is essential to consider attachments of tendons positioned on the proximal surface of the distal phalanges, because osteomyelitis has the potential to extend proximally via contiguous spread through adjacent tendons, thereby necessitating prompt diagnosis (Aragón-Sánchez et al., 2015).

The tarsal tunnel is a pathway through which pathogens progress into the leg, and severe infections characterized by rapid progression and risk of limb amputation or death. Timely surgical intervention of infectious ulcers decreases the likelihood of major limb amputation. An intensive surgical intervention against infections of the foot in diabetics significantly decreases progression to a proximal lower-limb amputation. Effective management of diabetic foot infections involves early surgical debridement alongside appropriate antimicrobial therapy (Pitocco et al., 2019).

Pathogenesis

The *C. perfringens* is able to produce 20 various toxins and enzymes released into the extracellular environment. Classification is primarily based on the organism's ability to produce six principal toxins: Alpha (CPA), Beta (CPB), Epsilon (ETX), Iota (ETX), Enterotoxin (CPE), and necrotic enteritis-β-like toxin (NetB). The bacterium produces seven toxinotypes (A to G). The Alpha toxin (CPA) is produced by all seven toxigenic types (A to G) of C. perfringens. Type A exclusively produces alpha toxin (CPA), whereas Type B also generates beta toxin (CPB) and epsilon toxin (ETX) in addition to CPA. The toxins, such as CPB, ETX, ITX, CPE, or NetB, have toxinotypes C, D, E, F, and G, respectively, each of which produces one additional specific toxin alongside CPA. Each distinct toxinotype has been linked to specific disease manifestations (Duc et al., 2024).

The pathogenic factors of *C. perfringens* can be classified as enzymes that disrupt cell membranes, toxins that form pores, toxins acting within host cells, and enzymes that break down biological molecules (Revitt-Mills et al., 2015). The location of genes encoding virulence factors could be on the chromosome and the large plasmid. Chromosomally encoded virulence determinants comprise the cpa gene (which encodes alpha-toxin), colA (κ-toxin), pfoA (θ-toxin), and nagH (hyaluronidase or μ-toxin). These genes are located within a polymorphic region of the chromosome (Chalmers et al., 2008).

The toxins that form toxins such as CPB, ETX, ITX, CPE, and NetB permit the influx of Ca^{2+}, Na^{+}, and Cl^{-} ions, while facilitating the efflux of K^{+} ions, resulting in depolarization of the electrochemical gradient, imbalance in ionic regulation, and subsequent cell death (Camargo et al. 2024). The pathogenesis presents with three well-characterized phases, independent of trauma-related origins of infection. The first phase, interruption of perfusion, which subsequently diminishes the redox environment, therefore properly fosters a setting in which bacteria can thrive. The second phase is presented with bacterial growth and initiating circumstances that lead to increased toxin production.

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Among the twenty identified toxins of *C. perfringens*, the major toxins and Perfringolysin O are the most significant in terms of their epidemiological impact and pathological effects (Grenda et al. 2023).

CPA (alpha-toxin) attacks the plasma membrane of host cells, producing sphingomyelin and phosphatidylcholine, which leads to both necrotic and apoptotic cell death (Hussain et al., 2024), as well as platelet aggregation, thrombosis, and histamine release (Buboltz and Murphy-Lavoie, 2023). It also reduces neutrophil maturation and activates arachidonic acid metabolism (Grenda et al., 2023)—increased death rate in GG patients related to alpha-toxin produced by *C. perfringens*. It additionally results in anemia by inhibiting and destroying red blood cells within blood vessels. Moreover, it releases inflammatory factors like TNF-α, IL-1, and IL-6 that drive to toxic shock, leading to reduced blood pressure and decreased cardiac function (Leiblein, M. et al., 2020). The CPA is also responsible for resulting in hemolytic and cardiotoxic effects. Additional virulence factors include collagenase, hyaluronidase, hemagglutinins, and hemolysins (Buboltz and Murphy-Lavoie 2023). The CPA consists of 370 amino acids and is divided into two domains: 1-249 amino acids in the catalytic N-terminal region and the membrane-interacting C-terminal region 247-370 amino acids. It encompasses adherence to the cell membrane, induction of hemolysis, and cytotoxic effects (Camargo et al. 2024).

CPB (Beta-toxin) forms pores that attach to endothelial cells and result in neurotoxic effects by triggering the release of substance P (Grenda et al.2023). Additionally, toxin has been extensively demonstrated to play a pivotal role in the complex pathogenesis and progression of necrotizing enterocolitis (Yao and Annamaraju, 2023). Camargo et al. (2024) mention that the CPB toxin is from the alpha-haemolysing family and composed of 336 amino acids, is thought to adhere to receptors or via the C-terminus to form oligomers (while the detailed structure-function correlation has yet to be fully understood).

ETX (Epsilon) results in advanced hemorrhagic enteritis and systemic shock resulting from enterotoxaemia in sheep. This toxin induces prominent perivascular edema accompanied by the swift onset of cellular swelling. Furthermore, it demonstrates the capacity to accumulate in organs such as the kidneys and brain. The ETX consists of three domains: first, the N-terminal domain, which facilitates receptor interaction; second, the central domain, which mediates membrane insertion and pore formation; and third, the C-terminal domain, which plays a role in proteolytic activation (Camargo et al.2024).

ITX (Iota) produces two separate proteins, namely Ia and Ib. The Ib component selectively binds to a specific receptor located on the host cell surface and subsequently facilitates the association or translocation of the Ia subunit into the cell, due to endocytosis. The Ia enters into the cytosol by membrane channel induced by Ib, and the actin cytoskeleton depolymerises via ADP-ribosylation (Grenda et al. 2023). The ITX belongs to the class of binary toxins, consist of the toxin is composed of an enzymatically active Ia component (454 amino acids) and a receptor-binding Ib component (875 amino acids), with a 243-base non-coding region separating the two. Both Ia and Ib show cytotoxic properties (Camargo et al. 2024). The ITX demonstrates fatal activity and causes dermal tissue necrosis in animals. The virulence factor of Ia depends on ADP-ribosyltransferase; the Ia mutants without ADP-ribosyltransferase activity cannot cause toxic effects with precedence of Ib in mice (Nagahama et al., 2023).

CPE (Enterotoxin) pore produces a toxin, which is capable of binding to claudin receptors on the surface of cells. Crucial for mediating calcium influx is the hexamer complex formed. The influx depends on dosage and is considered a calpain activator, therefore resulting in cell death. The CPE leads to food poisoning and non-food-borne diarrhea (Grenda et al. 2023). The CPE is composed of a single polypeptide chain containing 319 amino acids and is divided into three domains: the first binds to claudin-specific receptors, while the second and third make up the N-terminal portion linked to the ability to form pores (Camargo et al. 2024).

NetB (necrotic enteritis B-like toxin) is noted in cases of avian necrotic enteritis resulting in formation of pores (Grenda et al. 2023). The NetB is a putative gene responsible for synthesizing a

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323-amino-acid toxin protein, such as secretion signal for 30 amino acids, which exhibits 38% sequence identity with to CPB and results in necrotic enteritis β-like toxin, NetB naming (Camargo et al. 2024).

Perfringolysin O (PFO) as a pore-forming toxin, NetB and CPA exert enhanced pathogenicity through synergistic mechanisms on the pathogenesis of clostridial myonecrosis. The mechanism involves destroying red blood cells and leads to coagulative necrosis. Furthermore, this toxin shows resemblance with other pore-forming toxins found in *Streptococcus*, *Bacillus*, and *Listeria* (Grenda et al. 2023).

The study from Hassan et al., (2015) illustrates that comparisons of genes from 12 stains from numerous toxinotypes isolated from various sources revealed no distinguishing characteristics separating toxinotype A from the other strains. Highlighting the ability of toxinotype A to convert into other toxinotypes by acquiring plasmids that carry toxin genes.

The types A and C have been implicated in human diseases. Type A is causative of the majority of *C. perfringens* related to food poisoning and non-ingestive-source diarrheal disease. The consumption of undercooked beef is a known risk factor for *Clostridium perfringens* infection followed by chicken meat. The endemic enteritis necroticans in post-World War II Germany, also known as pig-bel from Papua New Guinea, is associated with infection by C. perfringens type C. The acute malnutrition increases vulnerability of patients to type C infection (Yao and Annamaraju, 2023).

The *C.perfringens* toxinotype A is considered as the most ubiquitous type of bacteria related to foodborne illness in the United States, Europe and Japan (Miki et al., 2008; Erol et al., 2008). The study by Duc et al., (2024) on *C. perfringens* samples isolated from pork and chicken meat in Vietnam were identified as type A. Comparable findings were made in research by Erol et al., (2008) in turkey meat in Turkey. Moreover, in Belgium, the 71 *C. perfringens* stains were type A (Gholamiandehkordi et al., 2009). However, (Afshari et al., (2015) reported that in Iran Type C was the predominant strain identified in broiler meat samples.

The type A results in GG and myonecrosis condition manifests with fever, pain, swelling, and advancing muscle tissue death, which can escalate to sepsis, toxic shock, and ultimately result in death. Proliferation of *C. perfringens* cells leads to extensive destruction of the affected tissues (Grenda et al. 2023).

The type B causes sheep dysentery and sometimes in cattle and horses. The disease leads to damage in the intestinal lining and toxins released in the gut enter the circulatory system, leading to enterotoxemia. The actions of CPB and ETX toxins resulting in dysentery in sheep is marked by necrohemorrhagic inflammation of the intestines (Grenda et al. 2023).

The type C mostly affects neonates because of reduced trypsin which offers innate protection from the disease. Diabetic individuals and those with pancreatic diseases are also affected. The disease manifests in an acute or peracute form and is frequently lethal (Grenda et al. 2023).

The type D is related to enterotoxemia and enterocolitis in animals such as: sheep, goats, and turkey, and sometimes cattle. The conditions manifest in lesions in the brain and other extra-intestinal organs. The consumption of food rich in fermentable carbohydrates makes animals more vulnerable to disease (Grenda et al. 2023).

The type E is mainly isolated from the bowels of ill animals. However, this stain inhabits the intestine if animal and presence of E stain do not indicate signs of illness (Grenda et al. 2023). The type E produces iota-toxin which consist of binary components: Ia and Ib (Nagahama et al., 2023).

The type F upon sporulation produces alpha-toxin and CPE , which are categorised as toxinotype A. The stains cause food-poisoning and non-foodborne diarrhea but also antibiotic-associated diarrhea. In the U.S., toxinotype F is identified as the second most prevalent foodborne pathogen (Grenda et al. 2023).

The type G is associated with avian necrotic enteritis, considered as the most common poultry disease. Infection with *Eimeria* spp. is widely recognized as the main predisposing factor for necrotic enteritis, the chicken being the most affected animal. Furthermore, other avian species such as: geese, ostriches, turkeys, quail, bluebirds, lorikeets, crows can also be affected (Grenda et al. 2023).

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Symptoms and Diagnosis

Clinical illustration of GG usually includes: elevated temperature, discomfort, swelling, and a malodorous, grayish or turbid wound exudate resembling "dishwater". Subcutaneous tissue, fascial networks, and profound musculature develop necrosis due to vascular insufficiency. While peripheral nerve damage may blunt pain sensation (Serafio-Gómez JL, et al. 2023). The diminished pain sensation in neuropathy is considered a classical clinical manifestation of infection. However, diabetic patients do not show signs of the typical manifestation of the neuroinflammatory cascade. The secondary signs in foot ulcers include: fragile or discolored granulation tissue, unpleasant odor, serous (non-purulent) exudate, and prolonged wound healing (Pitocco et al. 2019).

The patients usually present with exaggerated pain response compared to the apparent severity of the wound. Indicators of the severity of infection are characterized by sepsis signs, such as high fever, accelerated heart rate, and systemic hypotension. The patients with spontaneous GG exhibit heightened systemic manifestations of sepsis when compared with trauma-induced infections. Intensified early signs include swelling, altered skin tone, and tenderness in the affected area. Similarity of non-traumatic GG to traumatic GG is in gas production, which results in palpable gas crepitus of the infected tissue. Other complications in non-trauma-related GG include: the spread of pathogen to bone, causing osteomyelitis, and formation of gas-filled bullae in the skin of the lower limb (Hussain et al., 2024).

The GG patients with spontaneous non-traumatic type display prominent systemic symptoms of sepsis in comparison to the traumatic type. The site of infection in non-trauma-related cases presents with the sudden development of further complications, because of already contributing factors such as chronic illnesses that predispose individuals to infection (Hussain et al., 2024). Grenda, T., et al. (2023) found out that patients with non-traumatic GG have a shorter survival time, which is 8 hours, than those with traumatic cases, where survival time is 16 hours.

Medical professionals are advised to consider the possibility of GG if a necrotic wound located in soft tissue and muscle is present with anaerobic gram-positive bacilli (Buboltz & Murphy-Lavoie, 2023). Detailed physical examination of the infected area is crucial, crepitus resulting from subcutaneous gas accumulation can be revealed by palpation. Additionally, "appearance of the tissue, including color changes, blisters, and signs of necrosis" contributes to diagnostic accuracy. The finding of gas in infected tissue with GG tissue varies into several ways: while radiographic imaging modalities, including plain X-rays, can reveal gas accumulations, CT scans and ultrasound, on the other hand, allow direct visualization of intratissue gas, thereby illustrating accurate diagnosis and guiding treatment procedures (Hussain et al., 2024).

Treatment

Antibiotic therapy, along with diligent surgical cleaning of necrotic and devitalized tissue, forms the basis of treatment. The first line includes penicillin, clindamycin and metronidazole by Paquier et al., (2021) also vancomycin, tazobactam, carbapenem, or ceftriaxone by Buboltz and Murphy-Lavoie (2023). The spores, unlike vegetative forms of microorganism, are not destroyed from alcohol or chlorhexidine is commonly used to swab the skin before parenteral drug injection. The gluteal and pelvic regions are more prone to infection due to proximity to anus. Therefore, it is not the drug that is responsible, but the direct inoculation of spores, a risk heightened in individuals with diabetes, chronic corticosteroid therapy, or suppressed immunity (Paquier et al., 2021).

The Undersea and Hyperbaric Medical Society, (2019) described hyperbaric oxygen therapy (HBOT) as first mentioned in 1879. It is treatment for conditions such as: "delayed radiation injury, diabetic foot ulcers, carbon monoxide poisoning, decompression sickness and arterial gas embolism" (De Wolde et al., 2021). HBOT stimulates different growth factors which promote angiogenesis: EGF, hematopoietic growth factor, keratinocyte growth factor, PGF and VEGF. In diabetics HBOT decreases the eNOS which results in promoting angiogenesis and wound healing (Huang et al., 2020).

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The anti-inflammatory ability of HBOT was illustrated by reducing the concentrations of proinflammatory markers.The thermal imagining in HBOT shows the inhibition of temperature which indicates reduction in inflammation. This process is mediated by decreasing the NF-kB, the transcription factor promoting inflammation (De Wolde et al., 2021). Furthermore HBOT forms the reactive oxygen species ROS in tissue (Hussain et al., 2024). Increase in ROS indicates advanced pathogen clearance, growth of vascular endothelial factor, promoting angiogenesis and neovascularization (De Wolde et al., 2021).

Negative-pressure wound therapy NPWT is a technology that is used in treatment of large wounds. The process works though manual removal of necrotic debris, accumulated tissue fluid, pus, and pathogenic bacteria. The sealing prevents the engrave for additional infection contracted during hospitalization, superimposed on a primary disease (Paquier et al., 2021).

The study for STSG surgery to repair DFU wounds, divided patients into two groups.The first with undergoing NPWT and second undergoing alginate dressing change method. Patients undergoing NPWT demonstrated an increase in CD31-positive cells which promote angiogenesis, vasodilation and enhanced circulatory velocity. NPWT decreases the excessive number of Neutrophil extracellular traps (NET) which can damage the tissue. In moderation NET promotes antibacterial activity. However, myeloperoxidase generates hypochlorous acid and tyrosyl radicals, both of which can contribute to cytotoxic damage. Neutrophil elastase and proteinase 3 are capable of breaking down cytokines that play a supportive role in wound healing (Wu, Shen, & Hao, 2023).

The evacuation tube of NPWT can be used to remove the exudate and necrotic tissue. NPWT can be used in treating the superficial wounds and draining the deep wounds removing necrosis of tissue and decreasing bacterial growth and resulting in wound healing. The NPWT decreased mortality rate and complications of leg ulcers. The amputation rates were lower in groups receiving NPWT than conventional treatment (Wu, Shen, & Hao, 2023).

Although antibiotic therapy is effective for treating *C. perfringens* infection, due to the rise of antibiotic-resistant strains they are losing their efficacy (Grenda et al. 2023). The misuse and overuse creates antibiotic-resistance (Duc et al., 2024).

The study conducted by Duc et al., (2024) in Vietnam shows that high resistance-rate was observed in tetracycline (21/23; 91.30%), followed by clindamycin (10/23; 43.48%). Research by Beres et al., (2023) in food producing animals in Romania shows resistance to tetracycline was 71.4%. A study by Jang et al.,(2020) in Korean food shows 100% resistance to tetracycline. The lowest tetracycline-resistant stains were observed from poultry in Canada, 50% and 40% resistant to tetracycline and clindamycin respectively (García-Vela et al., 2023).

Conclusions

The GG remains a devastating issue for diabetic patients, resulting in tissue destruction, systemic toxicity, and high mortality rates. Effective treatment requires a multidisciplinary approach including strict glycemic control and addresses the infection with target antibiotics, HBOT, NPWT, and in severe cases amputation. In contrast, the non diabetic *C. perfringens* manifestations include the food-poisoning and non-foodborne diarrhea which historically affected children. The various animals affected by *C. perfringens* often result in antibiotic resistance due to widespread use of antibiotics, contributing to the emergence of multiantibiotic resistant strains.

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