

THE PITFALL OF DIABETES GANGRENE : ADVANCE IN PHARMACOTHERAPY

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ABSTRACT :

Blood glucose levels that are increased due to hyperglycemia, which is a chronic metabolic condition that gradually can seriously harm the heart, blood vessels, eyes, kidneys, and nerves. Those who have diabetes are more likely to have gangrene. This is because the condition's raised blood sugar levels can harm your nerves, especially those in your feet, making it simple to sustain an injury without experiencing it. Dry, wrinkled skin that ranges in colour from brown to purplish blue or black indicates this type of gangrene. Dry gangrene may take time to develop. People with diabetes or blood vessel disease, such as atherosclerosis, are more likely to experience it. wet gangrene develops when bacteria have infected the tissue, infection is referred to as wet gangrene.

INTRODUCTION :

Gangrene is the death of body tissue triggered by a major bacterial infection or a lack of blood supply. The toes and fingers, as well as the arms and legs, are frequently impacted by gangrene. It can also happen in the muscles and internal organs like the gallbladder. A condition like diabetes or atherosclerosis, which can stiffen the arteries and block blood flow, raises the risk of gangrene. Antibiotics, oxygen therapy, and surgery to recover blood flow and remove dead tissue are possible treatments for gangrene. The likelihood of recovery is higher the earlier gangrene is diagnosed and treated. Signs and symptoms of gangrene that affects the skin are- deviations in skin tone, from mild greyish to blue, purple, black, bronze, or red, Swelling, Blisters, Sudden, intense pain is followed by numbness. A sore that is releasing an offensive-smelling discharge & Skin became thin, clear, or hairless that is cool or frigid to the touch. Diabetes gangrene are of many types. A dry gangrene cause Dry, crumbled skin that ranges in colour from brown to purplish blue or black shows this type of gangrene. Dry gangrene may take time to develop. People who have diabetes or blood vessel disease, such as atherosclerosis, are more likely to experience it. A wet gangrene, if germs have infiltrated the tissue, gangrene is referred to as moist gangrene. Wet gangrene frequently has swelling, blistering, and a wet look. After a severe burn, frostbite, or other damage, wet gangrene can form. People with diabetes who unintentionally hurt a toe or foot frequently experience it. Wet gangrene must be treated right once since it spreads swiftly and has the potential to be fatal. Internal gangrene, which can be fatal if left untreated, affects one or more of the body's organs, including the intestines, gallbladder, and appendix. Internal gangrene happens when blood flow to an internal organ is blocked, as might occur if the intestines protrude through a weak spot of muscle in the stomach region (hernia), twisting. gas gangrene, Deep muscle tissue is frequently affected by gas gangrene. Your skin's outermost layer may first appear normal. The skin may start out pale and then develop grey or purple red as the illness advances. Skin may appear bubbly. The gas contained in the tissue may cause it to crackle when you press on it. Most

frequently, a bacteria called *Clostridium perfringens* causes gas gangrene. An injury or surgical wound without a blood supply is a breeding ground for bacteria. Toxins produced by the bacterial infection emit gas and kill tissue. Gas gangrene poses a serious threat to life, just like wet gangrene[41]. Fournier's gangrene, The vaginal organs are affected by this kind of gangrene. Although it typically affects men, it can also impact women. This kind of gangrene is brought on by an infection in the urinary tract or vaginal region[1]. Meleney's gangrene, this is an uncommon kind of gangrene. Usually, a surgical complication causes it. Typically, painful skin lesions appear one to two weeks after surgery. Progressive bacterial synergistic gangrene is another name for this illness. Factors that increase the risk of diabetes gangrene that are blood arteries may eventually get harmed by high blood sugar levels. A section of the body's blood flow can be slowed or blocked by damaged blood vessels; Blood clots and atherosclerosis, which harden and constrict the arteries, can both prevent blood from reaching a specific location of the body; Gangrene risk is increased by any condition that damages the skin and underlying tissue, including frostbite. If you have a health issue that affects blood flow to the damaged location, the danger is higher; Smokers are more likely to develop gangrene; The pressure of extra weight on the arteries can decrease blood flow, increase the risk of infection, and hinder the healing of wounds; The body's capacity to fight off infections can be impacted by chemotherapy, radiation, and several illnesses, including the human immunodeficiency virus (HIV); Rarely have injectable medicines been connected to gangrene-causing bacterial infections; issues with COVID-19. There have been a few cases of persons developing dry gangrene in their fingers and toes as a result of coagulopathy brought on by COVID-19. To confirm this connection, more study is required.

FOURNIER'S GANGRENE :

Fournier's gangrene (FG), a fatal and uncommon form of necrotizing fasciitis, affects roughly 1.6 men per 100,000 in the United States [1]. The death rate for FG is currently 40% [2], despite rigorous therapy, with literature estimates ranging from 20% to 80% [3]. FG is a quickly proliferating infection that affects the perineal, genital, or perianal regions and spreads through the superficial and deep fascial layers, leading to multiple organ failure and septic shock. The first person to find it was a French venereologist named Jean Alfred Fournier in 1883 [4,5]. *Escherichia coli* and *Bacteroides fragilis* are two examples of the numerous aerobic and anaerobic species that can produce the polymicrobial illness known as FG. These microorganisms work together to release the necrotic tissue-causing enzymes [6]. Collagenases, which are released by the bacterial organisms that cause this necrotic infection and hasten the progression of the infection from the vaginal region to the anterior abdominal wall and important organs [7], rapidly digest tissue at a rate of one inch per hour [3].

Even those who survive have urological and sexual impairments, and debridement frequently calls for repeated reconstructive procedures [3]. Additionally, tissue grafting is typically required during these operations as a way of reconstruction. Immunocompromised patients who are unable to absorb skin grafts and have slow wound healing are particularly affected by this [8]. Although FG can affect persons of all ages and genders, males between the ages of 30 and 60 are the most frequently affected [9]. A risk factor for FG is advanced age [2]. Patients with comorbidities like diabetes, alcoholism, atherosclerosis, peripheral vascular disease, malnutrition, prostate cancer, human immunodeficiency virus (HIV)

infection, leukaemia, and liver illnesses as well as individuals with no prior medical history are susceptible to developing FG [10].

Associated risk factor - FG has been associated with a number of both controllable and unmodifiable risk factors [2]. Modifiable risk factors are those that the patient can alter or regulate by medication or way of life modifications. This group includes chronic conditions like diabetes, substance misuse, and others. The patient's age is one example of a non-modifiable risk factor that cannot be altered. 52.7% of the patients in a study of 55 FG patients had concomitant conditions like diabetes, IV drug usage, liver failure, and immunological dysfunction. The usage of sodium-glucose co-transporter-2 inhibitors has been proposed as a potential cause of FG in diabetes, despite the fact that the precise mechanism behind this condition is unknown [33]. Furthermore, lesions are more prone to form in diabetics due to protein glycosylation and diabetic neuropathy. The potential for microbial organisms to breach intact skin during needle insertion is assumed to be the cause of the higher risk of infection among IV drug users. Through the use of needles, pathogens that are ordinarily difficult to enter deeper tissue can do so quickly, resulting in a variety of pathogenic processes. Additionally, once bacteria have been introduced, patients with weakened immune systems are less likely to be able to get rid of them. An immunocompromised state can be caused by immunosuppressive drugs, underlying disease processes including cancer and HIV, and old age. Cancer and autoimmune diseases are among the many illnesses that are treated with immunosuppressive medications. Additionally, they are given before to organ transplantation.[34]

EVALUATION OF FOURNIER'S GANGRENE-

Physical findings: Early diagnosis is essential because FG has an insidious beginning and 40% of patients first report with no symptoms [5]. One of the initial signs is pain in the vaginal or perianal areas with little to no obvious cutaneous damage [34]. As FG moves into the deep face planes, more obvious signs of infection become seen. Patients with erythematous develop deeper and more darkish skin tones. Towards the end of the infection, subcutaneous crepitus with a foul odour (caused by anaerobic microbial activity) may develop. The infection eventually turns into gangrene, which exhibits more glaring physical symptoms [35].

The testicles are frequently spared since they have a distinct blood supply from the penis and scrotum [36]. Clinical scoring systems: In a clinical context, scoring techniques are used to assess the risk of death and point doctors in the direction of the most effective treatments. Two scoring tests are employed: the Fournier's Gangrene Severity Index (FGSI) and the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC). These tests make use of biomarkers like serum glucose, C-reactive protein, sodium, potassium, creatinine, heart rate, and body temperature. A score of 6 or above on the LRINEC scale, which has a range of 0 to 13, indicates necrotizing soft tissue infections (NSTIs). The FGSI rates nine clinical factors from 0 to 4 to determine the chance of survival or death in an emergency[35]. Imaging: A variety of imaging techniques can be employed to show the presence of air and the spread of an infection. Standard radiography is a quick and helpful tool since subcutaneous emphysema affects 90% of FG patients [5]. Ultrasonography (US) is another device that can be utilised to arrive at a rapid diagnosis. On US imaging, the presence of subcutaneous gas in the scrotum and perineum manifests as a

"dirty" acoustic shadowing [37]. Computed tomography (CT) is the most accurate imaging technique for estimating the level of infection, allowing surgical teams to plan debridement appropriately [38]. Magnetic resonance imaging (MRI) should not be utilised to delay surgical procedures when other imaging modalities are insufficient to assess the degree of infection [37].

TREATMENT -

Urgent Surgical Debridement - It is important to remember that controlling FG successfully is really challenging. This is a result of the necrosis' quick progression and late identification brought on by vague symptoms. The basic guiding principles of therapy for treating FG are hemodynamic stabilisation, parenteral broad-spectrum antibiotics, and prompt surgical debridement, in which all necrotic tissue is removed until viable tissue is discovered [39]. The results of a clinical evaluation indicate that in order to stop the spread of infection, necrotic tissue must be removed as soon as possible [5]. Conversely, surgical debridement frequently leads in severe deficiencies and has an impact on wide areas. A delay in surgical debridement was linked to a considerable rise in mortality in a retrospective study of 72 FG patients [40].

Hyperbaric Oxygen Therapy - For a better prognosis in the treatment of FG, hyperbaric oxygen therapy (HBOT) may be an effective adjuvant [5]. This is based on the pathogenesis of FG, in which the hypoxia brought on by arterial artery thrombosis causes ischemia and necrosis, which facilitates the growth of anaerobic bacteria. Therefore, bacterial growth is slowed down by creating an environment with sufficient oxygen. Patients who are refractory to traditional therapies like sterile honey and maggots should adopt this therapy approach in addition to early surgical debridement. It is important to remember, though, that certain studies have found that individuals undergoing HBOT had a higher death rate [41]. This can be attributable to the fact that HBOT was given to patients who had more severe presentations. Bias is thus a possibility. Given the rarity of the condition, its inherent complexity, and the scarcity of HBOT chambers, it might be difficult to link the two (higher morbidity and HBO therapy).

Negative Pressure Wound Therapy or Vacuum - Assisted Closure-Vacuum-assisted closure (VAC) can be employed to improve physiological wound healing after surgical debridement of all necrotic tissue [23] while minimising the requirement for skin grafting reconstruction in the future [14]. Additionally, there is proof that it might hasten tissue healing [24]. The foundation of VAC is the negative pressure vacuuming that increases blood flow and causes inflammatory cells to migrate to the damaged area. As a result, granulation tissue forms and bacterial contamination, toxins, exudates, and debris are cleared away [23]. VAC therapy involves covering the wound with a transparent adhesive drape, a noncollapsible tube, and a sterile open-cell foam sponge.

A life-threatening infection like FG's necrotizing fasciitis requires urgent medical care. Given the virus's rapid progression, it is essential for doctors to swiftly identify groups at risk of contracting the infection and recognise the clinical symptoms in order to appropriately diagnose patients at an early stage. The most frequent clinical manifestations, according to this systematic review, were perineal discomfort, erythema, cellulitis, fever, abscesses, and crepitus. Depending on the infection stage, patients may appear with a wide range of symptoms or only a few. The results of our search included HBOT as well as unconventional medicines like sterile honey and maggots. The combination of broad-

spectrum antibiotics and urgent surgical debridement was the most successful treatment strategy for patient survival. Patient mortality in FG can be decreased with clinical training and early detection. Future study must focus on finding additional distinct criteria that can distinguish FG from disorders that present similarly because the presentation of FG can occasionally be ambiguous and nonspecific.

GAS GANGRENE :

Myonecrosis, also known as gas gangrene, is a highly fatal infection of deep soft tissue brought on by a variety of *Clostridium* species, the most prevalent of which is *Clostridium perfringens*. Since the Vietnam War era, the incidence of war-related wound infections has decreased to 0.1 percent due to advances in wound care, antisepsis, and the use of antibiotics. Clostridial myonecrosis was historically a common war wound infection with an incidence of 5 percent. Due to accidental inoculation of the surgical wound with gut bacteria, puncture wounds and surgical wounds, particularly those resulting from GI procedures performed on the biliary tract or intestinal surgeries, are causes of clostridial infections. [41][42].

Although they can happen on their own, clostridial infections typically develop in tissue that has been subjected to trauma. Patients frequently present with sepsis and the infection affects deeper tissue, such as a muscle, which can cause an infection to spread quickly along tissue planes. Following the initial trauma and inoculation, the infection may appear hours to weeks later. There are host and organism factors that affect the progression to infection, so the bacteria's inoculation does not always result in gas gangrene. Patients with compromised immune systems and those who have local tissue hypoxia (caused by trauma or inadequate vascular supply) are most vulnerable. *Clostridium perfringens*, *Clostridium septicum*, and *Clostridium histolyticum* are the most typical causative agents of these infections. C. The most typical reason for spontaneous gas gangrene connected to G is septicum. I. such as colon cancer, are abnormalities. C. perfringens as well as C. histolyticum are more frequently linked to infections after trauma. [43][44].

After a medical abortion using oral mifepristone and vaginal misoprostol, the uncommon pathogen *Clostridium sordellii* has been reported to cause fatal shock syndrome and gas gangrene of the uterus. As a result of the use of black tar heroin injections, also known as "popping," *Clostridium sordellii* is also becoming more prevalent. Infections following gynecologic procedures, such as septic abortions, which can result in gas gangrene of the uterus, and deep tissue infections related to childbirth have also been linked to this organism more frequently [41][45][46].

PATHOPHYSIOLOGY - C.perfringens causes 80 to 90% of gas gangrene cases, but other species can cause infections. In order of distribution, *Clostridium novyi* (40%), C. septicum (20%), C. histolyticum (10%), *Clostridium bifermentans* (10%), *Clostridium fallax* (5%) and C. Sordelia These organisms are found in soil and organic waste, especially when contaminated with faeces. A healthcare professional should suspect gas gangrene in the presence of anaerobic Gram-positive bacilli in wounds with soft tissue and muscle necrosis. Organisms produce gases that can be detected on X-rays or CT scans. Only about 5% of wounds colonized with *Clostridium* organisms become infected. Thus, host factors and the anatomical location of the inoculated organism help determine whether the bacterium will develop into a myonecrotic *Clostridium* infection. For example, a deep penetrating wound in the muscle tissue of an

immunocompromised host is more likely to develop infection than a host with a healthy immune system and good nutrition. Open, superficial wounds are less likely to become infected. This is especially true for deeper penetrating wounds or crushed, tissue ischemic wounds if properly cleaned and dressed.[49]

Theta and alpha toxins produced by clostridial organisms result in significant tissue damage. The infection can spread quickly, and within a few hours the patient could experience severe shock, sepsis, and eventually pass away. Because clostridial species are facultative anaerobes, a tissue that is better oxygenated with a 70mmHg oxygen tension will inhibit the growth of the organism. A facultative anaerobe is a type of organism that can switch from aerobic respiration to fermentation in the presence of oxygen. The clostridial organisms will proliferate more quickly if the tissue's oxygen tension is less than 30 mm Hg. Depending on the oxygen tension of the tissue and the quantity of organism inoculated, the infection can spread slowly over weeks or quickly over hours. [50].

The amount of exotoxins an organism produces determines how virulent it is; Clostridium perfringens is the most pathogenic with 17 known toxins, the most toxic of which is the alpha-toxin, a lecithinase. A phospholipase (lecithinase) called alpha toxin dissolves cell membranes, causing platelet aggregation, thrombosis, and histamine release. In addition, hemagglutinins, hemolysins, collagenase, and hyaluronidase are present. The inflammatory response of the host to the infection is blunted by theta toxins, which also directly damage the vascular system and cause leukocyte breakdown. Connective tissue is broken down by collagenase, allowing an organism to quickly spread across tissue planes. This is one of the main reasons why the infection can spread past connective tissue plains and into deeper muscle tissues.[45][51][52].

EVALUATION - CBC, CMP, urinalysis, PT, APTT, blood and wound cultures are all part of the immediate workup for a patient with suspected gas gangrene. In order to assess sepsis, which is frequently present in gas gangrene, additional blood tests like ABG, lactic acid, and pre-calcitonin may be useful. X-rays, a CT scan of the affected body part, and ultrasounds are common imaging tests. These can be useful in determining how severe the infection, abscess, and gas in the tissues are. Comprehensive lab and imaging work shouldn't put off surgically removing the necrotic tissue. At the time of the initial surgical debridement, a deep-wound aerobic and anaerobic culture can help identify the etiologic agent and guide antibiotic therapy. [57].

TREATMENT - Antibiotics, early surgical consultation with debridement, intravenous fluid resuscitation, ICU monitoring, and adjuvant hyperbaric oxygen therapy should all be used aggressively to treat patients because of the infection's quick progression. Given that this is a genuine surgical emergency, it is crucial to obtain early surgical consultation without delay. Instead of delaying the use of antibiotics to obtain cultures, healthcare providers should start using them right away. A carbapenem, ceftriaxone with metronidazole, or vancomycin and tazobactam are examples of reasonable broad-spectrum medications. Penicillin plus clindamycin, which also treats group A streptococcal necrotizing fasciitis, should be added if the healthcare provider suspects gas gangrene or a necrotizing soft tissue infection. Because it prevents the production of clostridial exotoxins and will lessen their systemic effects, clindamycin is a treatment option that needs to be seriously considered. Clindamycin should be combined with another antimicrobial drug like penicillin because it is bacteriostatic rather than bactericidal. [58][59][60][61][62].

To release compartment pressures, fasciotomy might be necessary. Further tissue ischemia and necrosis are sustained as the infection spreads into deep tissue along with the fascia. The goal of surgical debridement should be to eliminate all necrotic tissue as well as foreign objects like soil, debris, and shrapnel. It's crucial to apply a lot of sterile normal saline to the wounds as an irrigation solution. To increase survival, hyperbaric oxygen therapy should be combined with the standard treatment of antibiotics and surgical debridement. An intensivist, general surgeon, orthopedic surgeon, urologist (in the case of Fournier's gangrene of the testicles and perineal structures), gynecologist (in the case of uterine gas gangrene), infectious disease specialist, hematologist/oncologist, gastroenterologist (in the case of spontaneous gas gangrene), and hyperbaric oxygen therapy specialist should coordinate the care of these critically ill patients. Typically, a doctor from the emergency room initiates the consultation process after the disease has been identified early. [64][65][64].

Patients with a disease that would otherwise be almost always fatal can be saved with early IV antibiotics, early surgical debridement, and hyperbaric oxygen therapy. The fatality rate is reduced to about 30% with intravenous antibiotics and prompt surgical debridement of necrotic tissue. This can be decreased to 5 to 10% when hyperbaric oxygen therapy is added. Treatment for tissue ischemia, improvement of reperfusion injury to the tissue, and promotion of the activation and migration of stem cells and polymorphonuclear cells are all benefits of hyperbaric oxygen therapy. Additionally, it helps to improve the bactericidal effect of antibiotics and treats exotoxin production by bacteria. Additionally, the vasoconstriction caused by hyperbaric oxygen increases oxygenation while reducing tissue edema. The tissue's oxygen tension rises by a factor of 1000, and the increased oxygen content of the tissue aids in the resolution of hypoxia, enhances cellular activity, inhibits bacterial growth, and influences cytokinesis, which promotes neutrophil migration to the injured tissue. The production of growth factors like vascular epidermal growth factor (VEGF), which promotes neovascularization and tissue repair with capillary budding, is also increased by hyperbaric oxygen. This is usually observed following several hyperbaric oxygen treatments and is clinically recognized as increased granulation tissue formation. [66][67][68][67].

The patient is placed in a pressurized chamber for hyperbaric oxygen therapy, which can be mono-place (treating a single patient) or multi-place (treating multiple patients simultaneously). The attendant is outside the chamber with specialized equipment and pumps to run IVs and even mechanical ventilation equipment through ports in the chamber door or wall, and the mono-place chamber can only treat one patient at a time. The drawback of this arrangement is that it restricts the therapies that can be administered in the chamber, and if the patient needs to have direct contact with the attendant, the chamber must be depressurized and the patient removed. The multi-place chamber has the added advantage of allowing for simultaneous treatment of multiple patients, and the attendant is present in the chamber with the patients, facilitating easier access to the patient for chest tube insertion, ventilator support, IV therapy, and needle decompression of a pneumothorax. Three atmospheres absolute (ATA) is the recommended treatment pressure for gas gangrene. To help lessen the chance of oxygen toxicity, the patient will receive air breaks roughly every half hour. Usually lasting five to ten minutes, these air breaks. With 10 minutes for the ascent and 10 minutes for the descent, the treatment at pressure usually lasts a total of about 90 minutes. [64][69][70][64].

Treatments for gas gangrene begin twice daily for the first five to ten treatments, then decrease to once daily once the condition has stabilized. Beyond the initial stabilization, continuing hyperbaric oxygen therapy can hasten tissue healing and the body's readiness for eventual tissue grafting, which is frequently required to close the sizable wounds left after surgical debridement of dead tissue. The dangers of hyperbaric oxygen therapy include oxygen toxicity, which can result in seizures, hypoglycemia, particularly in insulin-dependent diabetics, barotrauma, which can harm the ears, lungs, or any gas-filled structures, like the stomach, and gas embolism. With the exception of ear barotrauma, which happens about 43% of the time (84%) and is most often caused by small tympanic membrane injections, these complications are uncommon. Gas gangrene is a serious emergency that must be treated right away, so it is essential to seek early surgical consultation. To obtain cultures, broad-spectrum antibiotics should be started right away. A third-generation cephalosporin (ceftriaxone with metronidazole), tazobactam, carbapenem, or vancomycin should all be included in reasonable coverage. Penicillin plus clindamycin should also be added to treat group A streptococcal necrotizing fasciitis in the event that gas gangrene or necrotizing fasciitis is suspected. We strongly advise using clindamycin. Hyperbaric oxygen (HBO) therapy is one of the adjunctive treatments for gas gangrene. Hyperbaric oxygen therapy has no effect on how the existing toxin functions, making debridement absolutely crucial. Patients who have hemodynamic instability might not be good candidates for HBO therapy. Furthermore, animal experiments studies were unable to prove HBO's therapeutic effectiveness. [71][72][70].

Providers should think about using negative pressure wound dressing therapy after sufficient surgical debridement has stopped persistent tissue necrosis.

CONCLUSION :

We advise stopping SGLT2 inhibitor use and starting a combination therapy with broad-spectrum antibiotics and surgical debridement right away if FG is suspected in a patient taking one of these drugs. The assessment and treatment of gas gangrene are described in this activity, which also emphasizes the importance of the inter professional team in enhancing patient care. In order to prevent and manage diabetes gangrene, the clinician must overcome numerous obstacles. Without a doubt, adopting a new lifestyle that includes dietary changes and increased physical activity is the first step in preventing diabetes. Additionally, it is well-known that the majority of patients find it challenging to maintain lifestyle changes. Therefore, it makes sense that any additional intervention, such as the use of pharmaceuticals, will follow. Although adding a pharmaceutical agent is simple, the risks and benefits must be weighed equally. Although metabolic disturbances that start early in life may increase the need for preventive therapy for much longer periods of time, there are concerns about long-term compliance and adverse effects, some of which are serious. The upside is the possibility of delaying or preventing the devastating effects of diabetes gangrene. Currently, the best strategy is for the doctor to spend enough time encouraging the patient to make appropriate and successful lifestyle changes and to make use of all the resources available to accomplish these goals. Pharmacological management may be necessary if the patient still has a high risk of developing diabetes and cardiovascular disease even after making sufficient lifestyle changes.

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