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MAJOR ANAEROBIC INFECTIONS OF THE FOOT

Clinical anaerobic infections of the foot are uncommon and the fact that they are rare is indeed fortunate since true anaerobic pathology is frequently misdiagnosed with devastating sequelae, such as limb loss, as reiterated by Mahan, Armstrong, Joseph, Marcinko, Sage and others, in 2005-2006 and beyond.

Historically, anaerobic pedal infections have not been referenced as extensively in the literature as their counterparts in the brain, mouth, breast, pelvis, ear, liver, lungs and intestinal tract. This may be due to the numerous confusing colloquial terms often ascribed to them. Terms such as "hospital gangrene", "gas gangrene", "acute hemolytic streptococcal gangrene", "anaerobic cellulitis", "necrotizing fasciitis", "vascular gangrene", "myofascial necrosis", "liquefaction necrosis", and the "fetid foot" are not entirely incorrect but do serve to obfuscate the correct medical definition of each specific entity. More basically, even the term "anaerobe" may be a source of confusion. By convention, an anaerobic organism is any microbe that requires reduced oxygen tension for growth and cannot grow on a solid cultural media, in an environment of 10% CO₂, in air (18% oxygen).

Since the tolerance of anaerobic bacteria to oxygen and oxidation-reduction potentials may vary greatly, there is tremendous latitude in this definition as many types of bacterial infections of the human body can involve anaerobes, given the proper clinical environment. For example, some anaerobes such as *Clostridium* (aka "septicum") and *Eubacterium* are "fastidious or "absolute"; while others such as *E. coli* are "facultative", growing in either the absence or presence of air; while others are "micro-aerophilic", such as *Actinomyces naeslundii* and *propionica*; while still others such as *C. perfringens* (aka *Bacillus aerogenes capsulatus*, *Bacillus phlegemonis emphysematosae* and *Bacillus perfringens*) are more tolerant to oxygen and possesses a higher oxidation-reduction potential.

Adding to bewilderment are certain other gram-positive cocci that prefer reduced oxygen tension but can still grow on solid media, and are termed "capnophilic". Thus, operative definitions are an important source of clarification when discussing the concept of anaerobic infections in the foot.

Morphologically, even the taxonomy of many anaerobes is changing. For example, some *Corynebacterium* are classified as *Propionibacterium* and some bacteria that have been implicated in actinomycosis (*A. propionica* and *Bifidobacterium eriksonii*) are no longer classified as *Actinomyces*. The nomenclature designation, "*Bacteroides fragilis*" or "Frank's bacillus", even includes other species

such as *B. vulgatus*, *thetaitaomicron*, *distasonis*, *ovatus* and *uniformis*.

Therefore, the purpose of this section is to provide a clinical overview of anaerobic foot infections. Covered topics will include clinical recognition, bacteriology, isolation and identification techniques, soft tissue and bone infections, specific pathologic entities, surgery, chemotherapeutics and adjunctive treatment

Patho-Physiology of Clinical Anaerobic Infections

Except for exogenously acquired infections such as clostridia from soil, earth or dirt, the majority of anaerobic infections are caused by organisms or toxins located within the human body and normally considered endogenous. Anaerobes are usually more plentiful other than microorganisms and outnumber aerobes 10:1 in the oral cavity and 1000:1 in the intestinal tract. The skin and integumentary system house *Propionibacterium* (anaerobic diphtheroids) and anaerobic Gram- positive cocci. The mouth, teeth, gums, lungs and upper respiratory system are sources of *Bacteroides melanogenics* and *Fusobacterium* species. The vagina is polluted with *Lactobacillus* while the perianal and perineal skin may be contaminated with intestinal flora. Clostridia is found on most mucus membranes, in the ear canal and perianal skin, the urethral meatus of both sexes and on the skin as a transient organism.

Still, all of these anaerobic organisms are beneficial in the human microbial ecosystem. For example, essential physiological roles include intestinal vitamin K synthesis by *B. fragilis* and *E. coli*, various essential deconjugated-dedehydroxylating bile acid transformation, and fat absorption and cholesterol reducing metabolic processes by the enterohepatic circulation. It is only when these invaders become pathologic that clinical symptoms ensues.

One major bodily defense mechanism is the normal oxidation-reduction (re-dox) potential (eH) of +120 mV. A lower eH permits anaerobic proliferation due to decreased vascularity, and the diminished tissue oxygenation it contributes, depending on the oxygen dis-sociation curve.

Fortunately, only a few hereditary or congenital defects exist which predispose to anaerobic infections and these do not impact greatly on the foot. Acatalsia however, is a rare genetic defect characterized by the absence of the enzyme "catalase", which results in recurrent infections of the gums, mouth and associated oral structures and may potentially seed into the lower extremities, in certain patients.

Clinical Scenario of Infection

The clinical scenario for a patient with a pathologic anaerobic infection of the foot is both immediate and severe. It is for this reason that delayed diagnosis or misdiagnosis is not uncommon. However, the historical inquisition and inevitable subjective and objective reactions are reliable characteristics for the perspicacious practitioner.

For example, even seemingly trivial incidents such as stepping on a nail, sustaining a small laceration,

puncture or scratch, legal or ill-legal drug injections, insect bites, frostbite, shock, minor foot surgery with or without epinephrine (low re-dox {eH} potential), foreign body implantation or contusion acqisitin, may be important historical findings when coupled with expressions of tormenting pain, anxiety or feelings of apprehension or impending doom. Neighborhood locales or recreational avocations contiguous to dairy, ranch, farm or other areas of fecal contamination may also be potential sites for anaerobic contamination, as well as decaying vegetable matter. Even more perplexing is the fact that the time frame from initial contamination, to clinical presentation, varies from as much as 2-30 days depending on the quantity of inoculum, virulence of the contaminating anaerobic agent(s) and health status of the individual patient. Preliminary physical examination frequently demonstrates a hot, red and swollen affected foot. Systemically, chills (although the actual fever may be low-grade), shakes, hypotension and the disorientation associated with the systemic signs and symptoms of any infectious process, may be seen. Pain out of proportion to the eliciting event is seen in the gravely ill and spiking febrile patient. The patient may appear emotional, anxious, apprehensive or frantic, and speak of an ill-defined feeling of death or "gloom and doom".

Demographically, patients of any age, race, sex or age may be affected, including infants and the elderly. Patients with peripheral vascular disease regardless of etiology, diabetes mellitus, obesity, herpes, lues, alcoholism, fractures, rheumatic conditions, malignancy, cortico-steroid dependency, AIDS or other immuno-incompetent disorders may be especially affected.

Integumentary changes are obvious and include smooth, shiny and taunt skin. Cellulitis, myositis or myonecrosis, gangrenous and infarcted tissue, with or without induration may be present. Vesicles, or blisters may appear and edema is of the non-pitting variety and extends beyond the portal of entry. A bronze, azure, indigo, dark or dusky purple ecchymotic color may be seen, at the site of the injury, progressing to frank infarction and gangrene after several days. Finally, decreased cutaneous sensation or anesthesia may provide pain relief to the patient, but signals a more serious impending soft tissue slough to the astute clinician. This sloughing phenomenon is a reliable clinical stigmata of the infectious process, especiaally in necrotizing fascitis, and is reminiscent of a high speed vehicular extremity degloving injury which leaves nothing but exposed skeletal bone, without the accompanying particulate foreign body implantation or fracture(s).

Other clues to the presence of clinical anaerobic foot infections may include a foul, putrid or rotten smelling (hydrogen sulfide) discharge; necrotic infarcted and gangrenous tissue with a "pseudomembrane"; black discoloration of blood containing exudates; "sulfa granule" discharges possibly indicative of actinomycosis; crepitant gas (carbon dioxide) in tissues, discharges or radiographs, MRI's or CT scans; infections following animal, insect, human or other bites; infections related to the use of aminoglycoside antimicrobial agents, septic thrombophlebitis, and antecedent other situations predisposing to anaerobic infections such as procedures on the GI tract, septic abortions or general surgery.

Laboratory Analysis

Laboratory evaluation may reveal acidosis and anemia as a result of erythrocyte hemolysis and a

plethora of bacterial endotoxins; jaundice also may be seen due to anemia with the potential for transfusion in acute cases; leukocytosis with a left shift of up to 30% and immature blast cell formations, although a lack of WBC's may itself indicate a clostridial infection; hyperbilirubinemia; hyper gammaglobulinemia with dark urine; hypocalcemia and hypoalbuminemia. In acute crises, septicemia may occur and estimates on incidence range from 2-10% of all cases, predominately from the non-spore forming gram negative rods such as Bacteroides. Clinically, the picture of bacteremia consists of a sudden onset, with rigors, chills, fever, diaphoresis and jaundice. Thrombosis and embolus formation are potential complicating factors. Additionally, Fusobacterium produces an endotoxin that may promote septic shock syndrome or a disseminated intra-vascular coagulation (DIC) phenomenon.

Specimen Acquisition, Cultural Techniques and Bacteriology

The continued improvement in specimen acquisition and cultural techniques will undoubtedly demonstrate the increasing prevalence of anaerobic infections in the lower extremity, particularly the diabetic foot. However, since most anaerobic flora associated with infections are benign, if not beneficial, misleading cultural data may be obtained. Therefore, the use of special acquisition techniques, transport containers, media and growth processing incubators are needed for appropriate isolation and identification.

Specimen Acquisition Techniques:

Specimen acquisition techniques include the procurement of a sufficient inoculum of material, in an expeditious manner, to avoid the destruction of fastidious oxygen sensitive organisms. Any abscess formation or intact instrumental layer should be decontaminated and detached removing purulent material with a syringe. Additionally, the most efficacious samples are taken from deep within wounds at the time of surgery thereby avoiding secondary or cross contamination. This method is preferred to a collection swab on a portion of exposed lesion, because saprophytic anaerobes unrelated to the infection may be obtained. Additionally, since pus is made up of dead white blood cells, it is not necessary to acquire a rich purulent specimen. Two other biopsy techniques may be helpful in questionable cases. The technique described by Uman and Kunin involves direct needle aspiration while another technique involves a limited and local surgical procedure to evaluate the subcutaneous stroma.

A frozen section for immediate diagnosis may also be attempted in selected cases. Criteria for diagnosis include: 1) superficial fascial necrosis, 2) venous and arterial thrombosis with angitis and fibrinoid necrosis, 3) dermal and fascial polymorphonuclear infiltration, 4) microorganism identification and 5) lack of muscular involvement.

After specimen procurement, a Gram stain with Darkfield examination is performed for preliminary identification and comparison with cultural data. Darkfield examination is helpful in demonstrating mobility, cellular morphology and certain non-Gram staining organisms.

Specimen Transportation:

Correct specimen transport is essential as it represents a weak link in the chain from specimen collection to identification. Resilient anaerobes may survive while more demanding anaerobes may perish, or facultative organisms that grow faster than anaerobes at room temperature may outlast more absolute anaerobes, producing skewed results if appropriate precautions are not made. For example, specimens may be taken to the laboratory in a syringe and needle, if no other anaerobic transport system is available.

After the specimen is collected, air is expelled from the syringe and the needle is inserted into a sterile rubber stopper. The method is not ideal and the specimen should be delivered to the laboratory immediately and set up to culture the sample within thirty minutes. Therefore, several more efficient and predictable commercially available transport systems are available for this purpose.

- A Vial Transporter is an anaerobic atmosphere glass diaphragm-stoppered bottle, which contained a solid pre-reduced agar mixture with eH indicator (sodium thioglycolate or amino triazole).
- The Anaerobic Bio-Plastic Bag Transporter may be used to transport, in its entirety, a specimen swab or syringe under sterile conditions. Upon closure of the bag, a gas generator, catalyst and indicator are activated in an anaerobic atmosphere.
- The Cotton Swab Transport Method utilizes a Pre-reduced Anaerobically Sterilized (PRAS) cotton tipped swab furnished in one tube and a medium column of semi-solid PRAS Cary-Blair medium in another. After collection, the swab is impregnated into the medium and firmly secured.
- A Transport Tube is a glass vial that is either flushed with CO₂ or placed in an anaerobic chamber for 48 hours and then sealed with a rubber diaphragm and foil cap prior to sterilization. It contains "resazurin", a redox (eH) indicator and a bit of pre-reduced peptone yeast medium. Samples are collected by a syringe and introduced through the diaphragm with a needle after expelling air from the syringe and needle lumen.
- E) The Vacutainer Anaerobic Transported is a double tubed, cotton swab, system. After collection, the swab is riposted into the inner tube, disengaging it into the central tube, simultaneously closing the puncture in the rubber stopper. The outer tube contains palladium-coated pellets which serve as a catalyst in the H₂, CO₂ and N₂ enriched environment. The H₂ combines with the O₂ to form water and generating an anaerobic atmosphere.
- An Anaerobic (Gas-Pack) Jar contains an envelope that generates hydrogen and carbon-dioxide after the addition of water, through the catalytic conversion of H₂ and O₂ to H₂O. The Jar is ideal for larger specimens and may be vented for an evacuation-replacement system to be used to acquire an anaerobic milieu.

Microbial Identification:

Following purity testing and isolate growth, organisms are sub-cultured to determine whether they are obligate anaerobes, facultative anaerobes, micro-aerophiles (*A. naeslundii*, *Arachnia propionica* and some positive cocci grow under reduced oxygen tension) or aerotolerant-philic (*Clostridium histolyticum* grows tenuously after initial anaerobic isolation). Tests for pathogenicity, toxin production and spore formation [may survive boiling in alkaline solution or dry heat to 150 degrees, for one hour] are then made for the identification of certain clostridia. This is especially difficult with *C. perfringens* and *C. ramosum*, with regard to spore formation, and *C. botulinum* and *C. tetani* with regard to toxin production. With sparse exceptions, Clostridia, lack the enzymes catalase, cytochrome oxidase, peroxidase and super oxide dismutase (SOD).

The identification of non-spore forming Gram-positive bacilli is also difficult and the current classification is based on the major acid products of glucose metabolism. For example, *Fusobacterium* species produce butyric acid while most *Bacteroides* species do not. However, *B. splanchnicus*, *putredinis* and *asaccharolyticus* produce smaller amounts of the acid but always in the iso-butyric and iso-valeric forms. Further species and sub-species classification is based on various idiosyncratic characteristics such as the presence of either desoxyxholate or bile, susceptibility to certain antibiotics or the fermentation of carbohydrates.

Anaerobic gram-positive cocci are divided into to genera, according to cellular morphology, while speciation is based on attributes such as indole production, carbohydrate fermentation and nitrate reduction. Some cocci types, such as the genus *Streptococcus*, even produce lactic acid as their major metabolite. Perhaps the most common anaerobic Gram-negative coccus is *Veillonella parvula* that does not ferment hexose but converts lactate to propionate and pyruvate to acetate and propionate. Other less frequently found anaerobic Gram-negative cocci are *Acidaminococcus fermentans* and *Megasphaera elsdenii*. Unfortunately, a lack of positive Gram stain or cultural data, is probably the rule, rather than the exception, when evaluating anaerobic infections.

Anaerobic Endocarditis

Levenson reviewed the standard medical guidelines for preoperative antibiotic prophylaxis when dealing with surgical patients considered to be at risk for aerobic endocarditis. However, no mention was made of anaerobic endocarditis as the incidence of this disorder is only slightly greater than 1-2% of all endocarditis cases. The population at risk includes patients over the age of 50 years, with a predilection toward older males, younger females and a tendency to spare children. Obviously those with rheumatic, congenital or degenerative heart disease are at increased risk.

The signs and symptoms of anaerobic endocarditis are not significantly different than those of other aerobic endocarditis types. Janeway lesions, for example, may occur in both forms. However, the rate of pulmonary embolism is higher and the incidence of preexisting heart disease lower, in anaerobic induced endocarditis than in endocarditis caused by facultative organisms.

The main portal of entry (POE) is the mouth, notably from poor oral hygiene, periodontal disease or following tooth extractions. Precipitating agents include *B. fragilis*, *Fusobacterium*, *Clostridium* (true

saprophytes) and Peptostreptococcus. In an update, the American Heart Association published its guidelines for the prevention of bacterial endocarditis. Recommendations for dental procedures and those involving the respiratory tract were put forth when Streptococcus viridans was the most common enterococcal pathogen. However, the overall effectiveness of prophylaxis remains undetermined.

In other studies, the potential for transient bacteremia from foot surgery, was evaluated in 42 non-cardiac risk patients. In no instance did bacteremia or septicemia result. However, despite these results, most authorities concluded that sampling of a larger population would be required before discontinuing prophylactic antibiotics. Currently, all patients considered at risk for developing aerobic or anaerobic endocarditis should receive antibiotics to prevent the onset or recurrence of endocarditis postoperatively. The antimicrobial agent is preferably administered prior to the procedure to provide optimal coverage and prevent development of resistant strains of organisms. The agents are bacteriocidal rather than bacteriostatic, with the particular exception in penicillin allergies which would require the administration of erythromycin. One such anaerobic antimicrobial agent is metronidazole (Flagyl-R) that shows consistently good bacteriocidal activity, "in-vivo" and "in-vitro".

Specific Pathological Entities of the Foot

In order to avoid confusion and promote disciplined order, the following specific conditions are cited, in a progressive fashion according to increasing severity and clinical morbidity.

Anaerobic Crepitant Cellulitis:

McLennan has defined anaerobic cellulitis as a localized soft tissue anaerobic infection that does not involve muscle mass. Although the condition may be characterized by a malodorous discharge and gas in the tissues, it does not induce great pain or edema and any discharge may be minimal with a small potential for systemic toxicity. Any gas producing non-spore forming or facultative anaerobes may produce the condition but an infection that involves clostridial contamination will be most severe. It is common in diabetic patients and treated with debridement and antibiotics, as described by Greenberg and Greenberg. Concomitant vascular compromise may necessitate radical resection or amputation. Prompt treatment prior to muscle involvement may lower the mortality rate by 20%.

Chronic Undermining Anaerobic Ulceration of Meleney:

Meleney's ulceration (MU) is an atypical soft tissue excoriation that is progressive, deep and spreads diffusely, producing multiple sinus tracts and necrotic foci from subcutaneous planes to the skin. Aerophilic streptococci are usual offenders. Treatment, with debridement and antibiotics, is infuriatingly slow.

Progressive Bacterial Synergistic Gangrene:

Progressive Bacterial Synergistic Gangrene (PBSG) is an unusual form of anaerobic infection. Common bacterial miscreants include Peptostreptococcus species and *S. aureus*, working in synergy to produce ulcerative necrosis of both skin, subcutaneous and fascial tissue plane.

Anaerobic Infected Vascular Gangrene:

Anaerobic infected "dry" Vascular Gangrene (AIDVG) is caused by anaerobic organisms in the face of an ischemic limb, from either generalized peripheral vascular disease or other local arterial flow compromise. In contra-distinction to anaerobic cellulitis, there is usually a great degree of edema with gas formation, but again there is only slight systemic bacteriemia capability. Facultative organisms such as *B. fragilis* or *perfringens* are common causative agents, not uncommonly from fecal fallout.

Necrotizing Fascitis:

Necrotizing Fascitis (NF) is a serious limb and life threatening infection that is noted for its rapid progression among soft tissue fascial planes. It was extensively investigated during the Civil War and became known as "hospital gangrene", acute hemolytic streptococcal gangrene" or "necrotizing erysipelas". The classic description of NF was provided by Meleney in 1924. Regardless of designation, the depiction of a dark-grey or ashen subcutaneous fascia remains a stigmata of a process that continues to possess a high morbidity and mortality rate due to major end organ collapse, acute septic shock, pulmonary embolism or DIC.

A list of differential diagnoses for NF includes erysipelas, streptococcal myositis, and the previously mentioned pathologic anaerobic entities. According to Mahan, diagnostic criteria for NF included: 1) extensive necrosis of superficial fascia with the undermining of surrounding soft tissue structures, 2) moderate to severe systemic toxicity with mental disorientation, 3) absence of clostridia as the predominant pervading pathogen, 4) absence of muscle destruction and major vascular occlusion, and 5) an intense leukocytic infiltrate on pathologic examination of involved necrotic structures. Consequently, the difficulty in establishing the diagnosis is based on the triad of non-existent or trivial trauma, confusing integumentary changes and rapid progression of the disease process.

Implicated micro-organisms include hemolytic streptococci, staphylococci, and *B. fragilis*, although a study of sixteen patients, by Pessa and Howard identified 75 species of both aerobic and anaerobic bacteria in wounds, while others have grouped NF into two types based on cultural data.

The first Type I contained both absolute and facultative anaerobes while the second Type II possessed group A streptococcus alone or in combination with staphylococci and in the absence of aerobes. Additionally, the use of oral non-steroidal anti-inflammatory agents has been associated with NF by Rimailho, Riou, Riachard and Auezpy.

Treatment of NF includes medical stabilization of the patient through electrolyte and transfusion supplementation, appropriate parenteral antibiotics, aggressive surgical incision and drainage with debridement, surgical re-exploration within 24-48 hours, nutritional support, and wound coverage by secondary or tertiary means. The use of IV fluorescein dye may assist in the determination of viable versus infarcted and necrotic tissue.

Myofascial Clostridial Necrosis (Gas Gangrene):

Myofascial Clostridial Necrosis (MCN), or "gas gangrene", is one of the most anxiety producing lower extremity infections for both patient and physician. Clostridial wound contamination is more common than realized and may approach 10-30% of all wounds in patients with diabetes or neoplastic disease. Typical clinical features include a painfully tense and pale edema, turquoise tinted ecchymosis, bullae formation, protracted necrosis, crepitant gas in 80% of soft tissue structures and eventual toxemia. Differential diagnoses include Synergistic Non-Clostridial Anaerobic (SNCAM) Myonecrosis (aka cutaneous necrotizing myositis or synergistic necrotizing cellulitis) and Anaerobic Streptococcal Myositis (ASM). SNCAM is a virulent soft tissue infection not involving bone. Extensive "liquefaction" necrosis may occur producing "dishwater pus". *Bacteroides* sp. (Gram (+) rod, spore formers or non-spore formers), anaerobic streptococci and other facultative Gram-negative bacilli are inculcated in this disease. ASM is characterized by pain, toxemia and seropurulent exudate with edema. Debridement, antibiotics and anti-gas gangrene antitoxin is often needed for successful treatment.

Human, animal or fecal fallout or farmland contaminations are archetypal environmental sources of gas gangrene contamination and blowflies may play a role in its transmission as a vector to humans. Etiologic agents include *C. perfringens* (aromatic gas producer with alpha toxin production), *C. septicum* (rapid symptom producer especially in patients with cecal carcinoma), *C. novyi*, *C. histolyticum*, *C. tertium*, *C. paraputrificum*, *C. sardiensis*, *C. butyricum*, *C. fallox*, *C. beiferinckii*, *C. ramosom*, *C. sporogens*, *C. capitovale*, *C. bifermentans* and *C. sartagoformum* (47). Nonclostridial aerobic culprits, which may also produce gas in tissue planes include: *K. pneumonia*, *E. coli*, *Enterobacter* and *Proteus* (Gram negative rods), *S. pyogenes* and *S. aureus* (Gram positive cocci).

The presumptive diagnosis of *C. perfringens*, type A, may be made by the presence of colonies on human, rabbit or sheep blood agar plates. It is characterized by nonmotile subterminal, oval spores, which can ferment sucrose with exceptional gas production known as "stormy fermentation", producing nitrates and sulfides. It is also known to produce eight minor toxins (theta {cardiotoxic}, kappa, {collagenase}, mu (hyaluronidase), Nu {deoxyribonuclease}, fibrinolysin {protease}, neuraminidase {splits tertiary sialic acid}, hemagglutinin {neutralizes blood group factor A} and circulating factor {inhibits phagocytosis}, and several enterotoxins.

The species can be subdivided into five types (A-E), on the basis of the four major toxins, known as alpha or lecithinase, beta, epsilon and iota. The development of a "double zone" of hemolysis when *C. perfringens* is grown on enriched agar, known as the Nagler reaction, is pathognomonic.

This occurs when the clostridial enzyme "lecithinase" or phospholipase-C attacks the egg yolk in the media and produce a clear opaque like area around bacterial growth, by splitting lecithin into diglyceride and phosphorylcholine. Typically, the inner zone is completely hemolyzed while the outer zone is usually incomplete. *C. paraperfringens* may also produce this reaction but is not often encountered in clinical practice.

Tetanus (Lockjaw):

Tetanus "trismus" or "lockjaw" is a noncommunicable infectious disease, caused by the pervasive, anaerobic Gram positive, spore forming resident agent of dirt and the bowel, *C. tetani*. The organism, *C. tetani*, itself is not invasive, grows slowly to the size of .5 um. X 2.5 um. and is harmless except for the production of a plasmid mediated neurotoxin (tetanolysin = oxygen sensitive and tetanospasmin = intracellular) which acts on the CNS to reduce inhibitory motor activity. Circulating blood levels of antitoxin less than 0.01 IU/ml. at the time of onset are indicative of diagnosis. The common route of transmission is a break in the skin (needle sticks, nails punctures, lacerations, animal bites, scratches, insects, bullet wounds) in an outdoor setting.

In the medical setting, common conditions associated with tetanus included gangrene, frostbite, ulcerations, osteomyelitis, and dental abscesses and procedures. Up to 40% of the human intestines are colonized with *C. tetani*. The clinical characteristics of tetanus were first described by Hippocrates, and then by Carle, in 1884, when the etiologic agent was first identified. Early clinical features of localized tetanus, within 3 days to three weeks of inoculation, include pains and spasm confined to the injured area. Generalized tetanic signs and symptoms include headaches, constipation, sweating, tachycardia, dysphagia, trismus with neck stiffness, Risus sardonicus, local and fascial cramps, ipsilateral hyperreflexia and anxiety. Cephalic tetanus occurs with lesions of the head and face and present with atonic nerve palsies III, IV, IX, X, and XII. It is more common in males.

Aggressive respiratory and supportive care, with sedation, is needed as demise is due to respiratory collapse. Moreover tetanus antitoxin and toxoid should be administered, at different sites, along with wound debridement and penicillin antibiotics. Descombey, in 1924, prepared a toxoid, chemically changed toxin, which induced neutralizing antibodies without inducing the illness and began the wholesale process of tetanus prophylaxis.

Gumann reiterated the following protocol of Karlin, regarding tetanus prophylaxis in open wound fractures.

Tetanus Prophylaxis Potocol

<i>Immunization Data</i>	<i>Course of Action</i>
Complete immunization with last booster with one year.	None needed
Complete immunization within last 10 years but no booster follow-up.	Administer 0.5 cc. tetanus and diphtheria adult toxoid (Td).

Complete immunization and subsequent booster within last decade.	Administer 0.5 cc. Td.
Complete immunization but no booster within last decade. Clean minor wound promptly treated.	Administer 0.5 cc. Td.
Complete immunization more than a decade ago with no booster within past 5 years.	Administer 0.5 cc. Td. and 250 units Human Tetanus immune globulin
Wound other than minor and/or not treated promptly.	(TIGH), at separate sites with separate syringes. Give 500 u. if wound is clostridia prone.
No record of immunization with clean minor wound treated promptly.	Start immunization with 0.5 cc. Td. and schedule further immunization.
No record of immunization with other than clean wound and/or treated promptly.	Administer 250 units TIGH and begin immunization with 0.5 cc Td. Give 500 units TIGH if wound is clostridia prone. Use separate syringes at separate sites.

Additionally, once the three-dose primary immunization series has been completed, along with at least one booster dose every 10-15 years thereafter, routine supplementary boosters at the time of additional injury are not needed. In fact, too frequent booster administration may increase the likelihood of hypersensitivity reactions to immunization. Tetanus toxoid is safe and immunogenic and protects through neutralizing antibodies.

Nearly all-primary recipients are protected. Interestingly, the under administration of tetanus prophylaxis in the USA appears to be the exception rather than the rule of care. Studies suggest that 1-6% of patients receive less than the recommended prophylactic amounts of Td (adsorbed tetanus toxoid) with or without TIG (Tetanus Immune Globulin) indicated by their clinical wound injury and historical review. On the other hand, 12-17% receive more than the recommended dose.

Tetanus Immunization Doses for Women of Childbearing Age

1. Early in Pregnancy or first contact.
2. Four weeks later.
3. Subsequent pregnancy or 6-12 months later.
4. Subsequent pregnancy or 1-5 years after dose three.
5. Subsequent pregnancy or 1-10 years after dose four.

Wound Botulism:

The concept of wound botulism was first noted in the early nineteen forties. Most affected patients were young males and wounds were often deep and avascular with associated osseous pathology. More recently, and increased incidence of wound botulism has been associated with intra-venous drug use or the chronic use of nasalar cocaine. Signs and symptoms include the usual GI and CNS stigmata of botulism. The diagnosis is confirmed with the isolation of *C. botulinum* from the infected wound or the presence of botulinum toxin in the serum. The fatality rate is about 16% but the prognosis improves with the availability of respiratory support. Local wound treatment includes surgical debridement, drainage and penicillin antibiotics.

Surgical Treatment of Anaerobic Infections

Appropriate surgical intervention is the initial therapeutic treatment in most anaerobic defilement. It is the "sin quo none" of therapy. In the initial acute condition, the simplest approach to wound care is extensive debridement of infective bone and soft tissue, under general anesthesia. A temperate finger-probing technique may be used to ascertain the extent of necrosis as infected soft tissue structures may distentegrate under slight pressure. The importance of aggressive and extensive "netoyagge" and resection of infected osseous tissue structures is essential, even if it approaches a radical intensity. Segments of necrotic skin, subcutaneous tissues, ligaments, muscles or tendons, as well as plantar fascia, may even have to be removed to expose the depths of the infection or to permit adequate drainage of tendon sheaths, tissue planes or the plantar vault. Fractures must be stabilized, and if large muscle mass loss occurs, or if limb function is seriously compromised, consideration must be given to amputation. Therefore, knowledge of the plantar arch architecture is vital since anaerobic organisms and necrosis may lurk in its associated spaces.

The plantar vault consists of three fundamentally segregated compartments; the medial (abductor hallucis muscle), lateral (abductor and flexor digiti minimi muscles) and central plantar compartments. The central compartment is further divided into medial (flexor hallucis longus, flexor hallucis brevis and adductor hallucis), superficial (flexor digitorum brevis, flexor digitorum longus, quadratus plantae and lumbricales) and deep chambers (interossei). The central compartment is still further subdivided into four laminated potential spaces, known as M1-M4, interspersed between the four definitive muscles layers of the foot. Therefore, as delineated by Bauer, this anatomic composition must be fully appreciated when tracking and exploring the infection process within the plantar vault.

Later, vascular reconstruction may be needed, although the infection management protocol usually comes first in a life-threatening situation. Of course, resected stumps, rays and feet will heal in time, if adequately perfused, but the prime objective of the surgery is to remove necrotic tissue and bone as

well as drain infection fluids.

Once the foot has been surgically decompressed, the next step in recovery involves daily debridement, and even a return to the operating room within 24-48 hours of the initial surgery. Liberal wound irrigation is also a helpful but often neglected portion of the debridement regime. Various solutions may be used such as normal sterile saline, hydrogen peroxide, or povidone-iodine in a concentration of one percent).

If the wound or cavity is significant in size, open wound packing with sterile gauze impregnated with iodophor or some other antiseptic that is not irritating to delicate granulation tissue, is indicated. However, aerobic infections are more prone to leave large cavities after debridement, while anaerobes are predisposed to destroy a more extensive but shallow surface area.

The encouragement of fluid removal is beneficial, as well as daily wound debridement and the avoidance of desiccation through the use of wet to dry dressings. Once granulation tissue begins to flourish, periodic gram stains and cultures are needed to evaluate wound progress in anticipation of healing. Delayed primary closure is usually not indicated in anaerobic corruption. These wounds must usually be packed open. Once the clinical setting and wound cultures do not demonstrate overt infection, temperature normalizes, and granulation tissue growth commences, the final stage of local wound management may begin, either by secondary intention, skin grafts or flaps.

Chemotherapeutics Agents and Antibiotics

Although surgical decompression is the treatment foundation for many infections, antimicrobial agents are also extremely important to reduce the likelihood of recurrent disease. Many infections in which anaerobes are established also involve facultative and aerobic organisms that will influence the choice of antimicrobial agents. Ecumenically, antimicrobial therapy for anaerobic infections will require high doseages and prolonged administration because of tissue necrosis and regression potential, and any agent may result in the superinfection overgrowth of non-susceptible organisms, including fungi. Therefore, the following is a list of common agents, as proposed by Dickinson and Lipkin, are used to treat anaerobic infections regardless of anatomic location.

Antimicrobial Agents of Choice

Penicillin G (natural penicillin) is active against many anaerobic infections including anaerobic Streptococci, Clostridia, Actinomyces and Fusobacterium but penicillin alone is not recommended for seriously ill patients and is not effective against *B. fragilis*. The usual dose is 1.2 - 24 MIL U/day. High doses of piperacillin, carbenicillin, amoxicillin and clavulanate, and ticarcillin and clavulanate, may be useful in some cases.

Most cephalosporins are less active against anaerobes than Penicillin G. Cefoxitin (MEFOXIN R) and cefotetan (CEFOTAN R) are active against most isolates of *B. fragilis* but no cephalosporin should be used to treat serious Clostridial infections. Some third generation agents such as ceftizoxime (CEFIZOX R) are moderately active against many anaerobes but offer no advantage over other agents for anaerobic infections.

The lincosamide Clindamycin (CLEOCIN R) inhibits bacterial protein synthesis by binding to the 50S ribosomal unit. It should not be used concurrently with other antibiotics that act in a similar manner, such as erythromycin and chloramphenicol. Plasmid mediated resistance has been reported in *B. fragilis*. Clindamycin is active against *B. fragilis* and other anaerobic microorganisms and Gram (+) cocci but not enterococcus or methicillin resistant staphylococci. Essentially, all aerobic Gram (-) bacilli are resistant. It is useful against *B. fragilis*, *C. perfringens*, *Fusobacterium* and anaerobic streptococci and as an alternative to penicillin in allergic patients. It is also more effective than lincomycin in terms of activity and oral absorption.

Metronidazole (FLAGYL R) is a nitro-imidazole compound that is metabolized by bacterial anaerobic nitroreductase with production of short-lived, cytotoxic intermediates that disrupt bacterial DNA. It is bactericidal and also affects certain parasitic organisms. Therapeutic uses include infections due to anaerobic gram (-) rods such as *Bacteroides* and *Fusobacterium*, including septicemia, osteomyelitis and septic arthritis. Some gram (+) obligative anaerobes and micro-aerophiles are resistant, along with most aerobic organisms.

Chloramphenicol (CHLOMYCETIN-R) inhibits bacterial protein synthesis by binding to the 50S ribosomal unit. Binding is competitively inhibited by clindamycin and erythromycin. Plasmid mediated resistance due to production of acetyltransferase enzyme as been recorded. It may also code for resistance to tetracyclines and ampicillin. Chloramphenicol demonstrates a broad spectrum of activity with variable antimicrobial affects against a wide range of Gram (+) and Gram (-) bacteria, chlamydia, rickettsia and *B. fragilis* induced anaerobic infections.

Finally, the tetracyclines inhibit bacterial protein synthesis by binding to the 30S ribosomal subunit but are generally not used in the treatment of anaerobic infections because of plasmid mediated resistant strains. Some clostridia, *F. varium*, aerobic cocci (microaerophilic cocci) and the *Eubacterium* are also resistant.

The aminoglycosides are considered inactive against the majority of anaerobic infections and their activity against enterococci is inadequate when used as monotherapy. It is important to note that penicillins may inactivate aminoglycosides "in vitro" and therefore should not be in the same solution or administered through the same IV line; dosing times should be altered as well.

Vancomycin (VANCOCIN R) is a complex glycopeptide derived from the actinomycete, *S. orietalis* and functions through cell wall inhibition. It is useful against certain anaerobic species and antibiotic associated enterocolitis caused by *C. difficile*. The anaerobic activity of the 4-quinolone ciprofloxacin (CIPRO R) is poor.

Gas Gangrene Antitoxin

Gas gangrene antitoxin was produced from hyper immunized horse plasma, which often produced a

sensitivity reaction. Then, a globulin modified polyvalent (*C. perfringens*, *C. histolyticum*, *C. sordelli* *C. novyi*) antitoxin was available, for a brief period of time. Both are no longer in vogue and the later is unavailable for general use.

Adjunctive Therapy

Hyperbaric oxygen (HBO) for anaerobic infections is controversial, but was promoted, by Malay. Essentially, it involves inundating the entire patient ("complete immersion") into an oxygen chamber with increased barometric pressure. Under this situation, the body acts as a liquid container and the three physical gas laws of Henry, Boyle and Dalton, exert their influence. This is to distinguish it from older more local modalities, which only encompassed the affected body part, and have since proven much less effective. The toxic effects of oxygen, on the lungs and CNS, are also mitigated in this fashion but pulmonary fibrosis (Lorrain-Smith effect) and eardrum rupture may still occur and myringotomy may be needed, in the unconscious patient, to equilibrate pressure changes.

Typically, the patient receives 20-25 treatments, three times per week, for duration of 60-90 minutes, at ninety pounds per square inch atmospheric pressure (1 atmosphere pressure = 14.7 lbs/in²). The outmoded mechanism of action was though to be directly related to the bactericidal activity of oxygen. Critics cite increased oxygen-radicals that may actually induce cellular injury. However, slight hyperoxia from oxygen radicals may antagonize rather than potentiate lipid peroxidation.

A more recent hypothesis suggests that an indirect mechanism of action is accomplished by increased neovascularization through white blood cell chemotaxis and phagocytosis with increased osteoclastic activity. Regardless, HBO remains an adjunctive modality, useful more for the residual effects of the anaerobic infectious process, than actual curative treatment.

Concluding Remarks

Anaerobic infections of the foot may cause significant morbidity and mortality in the affected patient. Acceptable treatment must include prompt diagnosis, appropriate surgery and therapeutic antibiotics. Long-term follow-up may also entail additional reconstructive surgical techniques to ameliorate the ravages of the pestilence. Therefore, the clinician must possess impressive protean skills in order to render adequate care to cope with this severe disease process. Moreover, knowledge of this material may also be important to know for board certification examinations.

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