CHAPTER 7

120-031

Clostridial Myonecrosis

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Traditionally, gas gangrene is associated with war.[11,31] However, a low incidence of gas gangrene (0.016%) was found during the Victnam conflict. Early and adequate debridement and delayed wound closure in front-line surgery explain the recent low incidence of gas gangrene in war surgery.[11] Although Hippocrates described gas gangrene,[27] we owe the most impressive description in early history to Fabricius Hildanus.[24] Also, Pare's well-known description of the wounded at the Siege de Rouen is suspect for gas gangrene.[35] Excellent reviews on the history of gas gangrene can be found in the literature.[4,29,35] The first report on organisms that can live and reproduce in the absence of free oxygen comes from Pasteur.[41] In 1871, Bottini demonstrated the bacterial nature of gas gangrene, but he could not isolate the causal microorganism. In 1892 Welch and Nuttall isolated *Bacillus aerogenes capsulatus (Clostridium perfringens* or *C. welchii)*, the microorganism most frequently involved in gas gangrene.[53] Novyi isolated the *Bacillus oedematiens* or *Clostridium novyi*.[40]

Treatment of gas gangrene with hyperbaric oxygen was introduced in 1960 by Boerema and Brummelkamp from Amsterdam.[7]

ETIOLOGY AND PATHOPHYSIOLOGY

Clostridial spores instead of the vegetative form of the bacterium are responsible for contamination. The source of bacterial spores is either exo- or endogenous. Nearly all exogenous infections occur in patients with compound and complicated fractures with extensive soft tissue injuries after street accidents. Only a minority are seen after a "sterile" operation, intravenous infusion, intramuscular injection, and criminal abortion.

Clostidial myositis as an endogenous infection is caused by contamination from a clostridial focus in the body, e.g., infection of the abdominal wall after

African deserts, it is found naturally all over the world in soil and dust and can be isolated in healthy persons from stomach, gallbladder, small and large intestine, vagina, and skin. *C. perfringens* is not a strict anaerobe; it grows freely in oxygen tensions up to 30 mm Hg and has restricted growth in tensions up to 70 mm Hg.[4] It does not form spores in tissues. Laboratory identification of *C. perfringens* is performed by either the Nagler reaction or the Lecito-vitellin (LV) reaction.[54] More than 20 different exotoxins produced by clostridia have been identified; 9 of these exotoxins are responsible for local and systemic changes in gas gangrene and are produced by *C. perfringens:* alpha toxin, theta toxin, kappa toxin, mu toxin, nu toxin, fibrinolysin, neuraminidase, "circulating factor," and "bursting factor." Alpha toxin, the most important, is an oxygen stable lecithinase-C that is hemolytic, tissue-necrotizing, and lethal.

Probably the other toxins are ancillary to alpha toxin and give rise to hemolysis, causing anemia, jaundice, and renal failure by hemoglobinuria, tissue necrosis, and serious systemic effects such as cardiotoxicity and brain dysfunction. Other exotoxins are synergistic and enhance a rapid spread of infection by destroying, liquifying, and dissecting healthy tissue. Alpha toxin can be fixed to susceptible skin cells in 20–30 minutes, is detoxified within 2 hours of its elaboration, and causes active immunity with production of a specific antitoxin.[55] The progressive nature of gas gangrene depends on the continuous production of alpha toxin.

A further subdivision can be made in clostridia that are toxogenic and proteolytic. *C. perfringens, C. septicum, C. novyi,* and clostridia that are believed to be only proteolytic. *C. histolyticum, C. bifermentans, C. sporogenes,* and *C. fallax* that augment an infection by their proteolytic capabilities, but do not cause the classical gas gangrene syndrome. *C. tertium, C. sphenoides,* and *C. sordelli* can be considered as contaminants. It is not known what these microorganisms add to the disease process.

CLINICAL PRESENTATION OF GAS GANGRENE

The incubation time of gas gangrene varies from 1 hour[33] to 41 days.[3] Kiranov studied gas gangrene in Bulgaria between 1964 and 1977. In 87% of cases in wartime, gas gangrene started 4 days or less after injury. Time between onset of gas gangrene and injury in peacetime was longer.[30]

Patients who are at risk for infection in general (e.g., patients with predisposing factors such as ischemia, diabetes mellitus, lowered resistance, foreign bodies, etc.; patients with underlying systemic diseases; elderly people; debilitated patients with gastrointestinal, biliary, or genitourinary tract infections; drug addicts; etc.) are also more vulnerable to gas gangrene. A high level of suspicion and the knowledge that, however rare and trivial the occasion, gas gangrene may occur, are imperative.

The local picture of gas gangrene is not like that of other pyogenic infections, which usually begin with a red erythematous discoloration of skin. In gas gangrene, the erythematous discoloration is subtle. Then, later, a rapidly progressive phlegmon appears. One of the first signs is extreme pain in the wound area, which is in sharp contrast to the minor local signs. Upon examination, at first one cannot imagine that the patient suffers such severe pain. The wound area appears quiet. This disproportional pain was noticed by Fabricius Hildanus.[24] In a very short

time, the extremity swells enormously, and the initially pale skin becomes tight and shiny. (Fig. 7.1). A watery thin, red-brownish wound exudate may appear. The gas produced by the bacteria (from carbohydrates) is so delicately dispersed in the muscle tissues that it cannot be felt. At this stage, the gas can only be seen on x-ray as featherlike figures between the muscle fibers (Fig. 7.2). This was observed by Savill as early as 1916.[44]

The next phase is a highly progressive and centripetal bronze or copperlike discoloration of the skin, also known as bronze erysipelas, that is darkest in color near the wound area while the wound margins and protruding muscle tissues are brown-black, showing myonecrosis. Tension in the tissues may be great enough to restrict arterial circulation and lymph drainage. From that moment on, there is an even more aggressive progression of the phlegmon. The progression of skin discoloration with tissue necrosis and hemolysis, together with the deeper localized myonecrosis that lies a bit behind, can be astounding. In one patient, we measured 25-cm progression in 45 minutes. Progression is most aggressive in arteriosclerotic, diabetic, or traumatic vascular insufficiency. In this phase of the disease, the border of gas forming in the tissues is often ahead of discoloration and necrosis. The gas is palpable, with a crackling sensation like walking in dry snow, in the tense tissues proximal to the discoloration. Soon thereafter, skin may become dark brown, and blue-black bullae (Figs. 7.3 and 7.4) filled with clostridia-containing sero-sanguinolent fluid may appear. The extremity spreads a typical sickly sweet odor. Without treatment, the patient dies quickly.

Signs and symptoms depict an overwhelming process. After the initial stage of extreme pain in the wound area, the body temperature rises within 12 hours to about 41 °C. This is still the early edematous stage without discoloration of tissues. Blood pressure falls, pulse rate quickens, and septic shock develops. The erythrocyte sedimentation rate (ESR) is low, and the leukocyte count is increased to $20-30/10^9/l$.

Moreover, there is a kind of psychiatric-neurologic complex of symptoms, characterized as toxic psychosis or symptomatic psychosis. The patient becomes dull and confused, which may progress into coma or delirium. Nora et al. demonstrated a direct effect of alpha toxin on phospholipids of the tissues of the central nervous system. He concluded that symptomatic or toxic psychosis is caused by the direct influence of circulating alpha toxin on the central nervous system. This view is supported by our experience that the condition of patients improves rapidly when they are treated with hyperbaric oxygen. Edematous swelling of brain tissue and degenerative cell destruction have been described.[39] Jaundice, partly caused by hemolysis by alpha toxin and partly by hepatic insufficiency, can be found in 25 – 50% of the patients.[43] Clostridia are also found in blood cultures. The overall picture of a hemorrhagic state after alpha toxin injection is caused by diminution of platelets, alteration of clotting activity, liberation of heparinoid substances, damaged capillary and epithelial cells throughout the body, and by the toxin influences on the liver and alteration of plasma proteins.

Impairment of kidney function is frequently seen in gas gangrene and varies from slight to moderate increase of blood urea, oliguria, or complete anuria, necessitating hemodialysis. One of the most important factors in the onset of impaired kidney function is the hemolytic-uremic syndrome.[43] Septic shock degrades kidney function still further.

Almost every patient with gas gangrene is anemic because of hemolysis by

circulating alpha toxin. Close monitoring and, if necessary, immediate correction of the electrolytic and fluid balance are mandatory. Many other complications due to the primary disease can be expected and must be adequately treated as early as possible. Complications such as adult respiratory distress syndrome after severe trauma, fat embolism syndrome in long bone fractures, deep vein thrombosis in patients who are immobilized for a long time, myocardial irritability by circulating clostridial endotoxins, and disseminated intravascular coagulopathy are often seen in serious infections.

DIFFERENTIAL DIAGNOSIS

McLennan divided histotoxic infections into those that are traumatic and those that are nontraumatic. In his classification, a distinction was made between anaerobic cellulitis and anaerobic clostridial myonecrosis. He defined anaerobic cellulitis as a clostridial infection that involves only necrotic tissue killed by ischemia and by direct trauma and does not invade healthy tissue. Anaerobic clostridial myonecrosis (true gas gangrene) was described as an acute invasion of healthy living tissue not damaged by previous trauma or ischemia. McLennan proposed the following classification:

Traumatic wound infections
- Simple contamination
- Anaerobic cellulitis
- Anaerobic myonecrosis
  - Clostridial
  - Nonclostridial

Nontraumatic wound infections
- Idiopathic
- Infected vascular gangrene

"The infected vascular gangrene has frequently, if inexcusable, been confused with gas gangrene and in view of its benignity, chronicity, and ease of treatment, must be carefully excluded."[31] It should, however, be borne in mind that vascular gangrene infected with clostridial organisms may, under certain circumstances, e.g., as a complication of an operation upon an extremity, give rise to acute clostridial cellulitis or myonecrosis in the previous healthy part of that extremity.

Hitchcock et al.[28] differentiated clostridial infections into (1) spreading diffuse myositis, (2) localized myositis, and (3) cellulitis. Although this division may be of value, there is still the possibility that an apparently localized myositis can progress into a spreading diffuse myositis. Altemeier's classification of clostridial infections is similar to that of Hitchcock, but he added tetanus, which is no longer an indication for hyperbaric oxygen.[17] Brightmore described a number of nonclostridial gas-forming infections in the perianal region, besides Fournier's gangrene.[8] A third classification was proposed by Darke et al., who differentiated gas gangrene and related infections as (1) clostridial gas forming, (2) clostridial nongasforming, (3) clostridial uterine, and (4) nonclostridial, with a distinction between streptococci and *Escherichia coli*.[12]

We use the following classification:

Anaerobic soft tissue infections
- Anaerobic cellulitis
  - Clostridial
  - Nonclostridial
- Necrotizing fasciitis
- Anaerobic myonecrosis
  - Clostridial
  - Nonclostridial

Since clostridial myositis is generally called gas gangrene, we may assume that the formation and presence of gas in the tissues are valuable diagnostic tools in establishing the diagnosis. All bacterial and nonbacterial disorders with tissue emphysema should, therefore, be included in the differential diagnosis.

Nonbacterial causes: All traumatic and chemical nonbacterial causes of soft tissue gas should be investigated when soft tissue crepitance is present without local or systemic signs of infection. Mechanical and traumatic sources of gas include excessive undermining of tissue planes during operation, which results in air entrapment. Air can also leak into tissues from defects in the esophagus, respiratory tract, and gastrointestinal tract. Excessive manipulation during surgery may cause gas in the operative site; however, this gas decreases rapidly. Air leakage after perforation of the esophagus is usually closely related to endoscopy and/or dilatation, or to spontaneous perforation. Air leakage from the respiratory tract is usually caused by trauma or by chest tube insertion. We have seen three patients with soft tissue gas after wound irrigation with hydrogen peroxide who had been referred on the suspicion of gas gangrene.

Other causes: There are several other severe nonclostridial crepitant infections, both aerobic (*E. coli, Klebsiella, Enterobacter,* and *Pseudomonas*) and anaerobic (*Peptostreptococcus, Bacteroides*).[1,6,12,13,21,36,49] In almost all cases of gas-forming infectious processes, soft tissue gas can be ascertained by clinical investigation alone. Upon examining the infected area, a crackling is felt. Sometimes x-ray of the infected area is necessary to confirm the diagnosis. We obtain x-ray pictures as a standard procedure, because we consider the specific featherlike distribution of gas in the muscle tissue to be a significant diagnostic tool.

DIAGNOSIS

The diagnosis is based on clinical and bacteriologic findings. Myositis and myonecrosis are important clinical signs, as is gas on x-ray. Only in the case of infection with *Clostridium novyi (C. oedematiens)* is gas in the muscles absent.[20] Because the novyi alpha toxin affects vascular permeability,[33] edema is more prominent. In gas gangrene caused by *C. novyi,* discoloration of the skin may be more purple than the copper- or bronzelike color present in other clostridial infections.

Blood and/or wound cultures must be positive for at least one of the pathogenic clostridia. Most of the time, myositis and myonecrosis are so overwhelming that, if present, other microorganisms hardly play a role in the early stage of the disease. After the gas gangrene is cured, these microorganisms may become more

significant.[10] A Gram strain shows massive, gram positive short club-shaped rods, sometimes with terminal spores, without leukocytes. Samples for culture and specimens for histology should preferably be taken at a distance proximal to the center of the infection or wound area, and not from apparently dead or healthy muscles. Samples for bacteriology should be taken from deep muscle tissue because superficial smears are of little value. For diagnosis of a gas-forming infection, needle aspiration can be done from the involved area, together with careful clinical inspection of the extent of infection. Needle aspiration has to be performed under sterile conditions from deep-lying muscle tissue and should be stored immediately in a special transport vial for anaerobes. Gas chromatography can show alpha toxin in the blood of patients with gas gangrene. This method is not yet routinely used.

PROPHYLAXIS OF GAS GANGRENE

Prevention of gas gangrene can be achieved by measures directed against the source of infection and by proper wound management and wound care. General hygienic measures for both patient and doctor, combined with prophylactic treatment of the patient, to reduce contamination with clostridia to an ultimate minimum are essential. The best prophylaxis against gas gangrene in wartime was a good soap bath and clean clothing the night before an attack.[23] In this respect, showering drastically reduces the number of microorganisms.[13] Prophylactic treatment consists of proper wound care and antibiotics; gas gangrene antitoxin is obsolete. In exceptional cases, hyperbaric oxygen can be used as a prophylactic.

General Wound Care and Management

Etiologic factors in the onset of gas gangrene are, in general, the same as those in nonclostridial surgical infections. They are (1) the presence of microorganisms, (2) dead space, and (3) necrotic tissue including collections of bile, serum, and lymph. In particular, wounds involving deep muscle areas with extensive laceration and devitalization with impairment of the main blood supply are highly vulnerable. So are injuries of the buttocks, thighs, legs, and finally, to a lesser extent perhaps, the shoulders.

The condition of the wound is far more important for the onset of gas gangrene than is the presence of clostridial spores. Circulatory insufficiency in the wound area causes a lowered oxidation-reduction potential, thus creating favorable conditions for clostridial spores to develop into the vegetative form. A basic element for the prevention of infections is proper surgical management, together with antibiotics (preferably a combination of antibiotics directed to both anaerobes and aerobes).

As prophylaxis against gas gangrene, penicillin-G in high dosages can be recommended (6–20 million units/day). If used at all, antibiotics should be continued for at least 5 days because, although the risk of gas gangrene decreases, it still remains present during the whole period of wound healing and recovery.

The following guidelines in wound management should be considered:

1. Adequate, particularly early and meticulous, debridement of wounds, especially in high-risk patients

2. Meticulous hemostasis
3. Deep wounds left open and adequately drained
4. Tight dressings and tight plaster casts avoided
5. Frequent use of colostomies in patients with deep-penetrating wounds of buttocks or upper legs, decubitus ulcers, and perianal and ischiorectal abscesses
6. Delayed closure in traumatic wounds and after lower-leg amputation, especially in patients at risk, perhaps even when the blood supply to the level of amputation has been considered to be sufficient at operation

A general rule as to the initial treatment of open fractures is difficult to give. The best policy seems to be to refrain from immediate internal fixation in patients at risk, unless a completely stable general and local situation can be reached. In these circumstances, it is better to use a form of external fixation, because stabilization of fractures is necessary in the prevention of infections. Delayed osteosynthesis has been advocated as a safe and tissue-saving way of treatment. This involves a few days' delay, during which time the soft tissues can recover from local shock and can be properly judged for viability, whether or not treated with hyperbaric oxygen during this period. If early osteosynthesis is preferred or high-risk conditions are present, delayed wound closure is advisable. Every surgeon has to realize that the possibility of gas gangrene exists despite all of the therapeutic and prophylactic measures outlined here.

Antibiotic Prophylaxis

Penicillin in high quantities is the best prophylactic agent. Even so, clostridial myositis has developed in patients treated with it. Chloramphenicol and erythromycin are also being used. In theory, vancomycin and metronidazole are effective although the results of their clinical application are not known. Tetracycline and clindamycin are not recommended because of the relatively common resistance of clostridia, although there are studies mentioning a 100% sensitivity of clostridia to clindamycin. When risk factors so indicate, penicillin prophylaxis should be given as early as possible.

The question remains, what should be considered a severe wound prone to develop gas gangrene? The answer is difficult because of the characteristic unpredictability of gas gangrene. We often encounter totally unexpected gas gangrene, e.g., after operations that could be considered completely "sterile" (stripping of varicose veins). Penicillin also has its risks. Very high doses (over 20 million units/day) may cause hemolytic anemia and very serious coagulation disorders.[48,51]

As a rule, short-term high dosage of antibiotics is recommended in wounds prone to infection. Although penicillin is the drug of choice, complications, as well as the risk of allergic reactions, make it not advisable to treat all serious wounds with this antibiotic. The attending surgeon must individualize each case to weigh the risk of gas gangrene against the risk of penicillin complications.

Hyperbaric Oxygen

Although prophylaxis with hyperbaric oxygen is not recommended in every patient at risk for gas gangrene, this modality may be considered in patients with

serious anaerobic contamination and in cases where the circulation is either disturbed or at risk. In particular, hyperbaric oxygen should be considered after reimplantation of extremities, reconstructive vascular surgery for open fractures with vascular damage (e.g., high-velocity bullet wounds), amputation for arteriosclerotic and/or diabetic gangrene, etc.

Type of Patient

Factors putting patients at risk for the onset of gas gangrene are:

Ischemia, traumatic vascular damage, and arteriosclerotic and/or diabetic arterial insufficiency

Lowered resistance by drugs (addicts); starvation; systemic underlying diseases such as diabetes mellitus, lupus erythematosus, rheumatic fever, inflammatory bowel disease (Crohn's disease, ulcerative colitis), malignancies, immunodeficiencies (either idiopathic or caused by corticosteroids, as in transplantation patients with liver and/or kidney function failure)

Foreign bodies (plates and screws after osteosynthesis, bone cement, sutures, etc).

Special attention should be given to patients who underwent:

Osteosynthesis after an open, compound fracture with contamination of the wound area

Lower-leg (or even upper-leg) amputation for diabetic and/or arteriosclerotic arterial insufficiency

Hip surgery, especially in elderly patients

Large bowel surgery

Surgery for acute cholecystitis and/or cholangitis

Repeated injections with epinephrine or epinephrine-containing compounds (contraindicated in areas with already compromised circulation)

Operations for small and large bowel ileus

Drug addicts with infections (including streptococcal myositis or myonecrosis) that can be accompanied by compartment syndromes, postabortion infections, and perineal and ischiorectal abscesses

TREATMENT OF GAS GANGRENE

In most cases, we are faced with seriously ill patients in need of intensive care. In addition to the specific treatment directed to the causative microorganisms, general supportive measures are to be taken. In general, these concern the maintenance of tissue perfusion and oxygenation, monitoring of fluid and electrolyte balance as well as blood pH, control of central venous pressure or pulmonary wedge pressure, etc. Particularly in gas gangrene, clinical estimation of fluid loss by wounds, mucous membranes, etc., is important. Patients are invariably in need of blood transfusion, due to hemolysis caused by clostridial toxin. Whole blood or an adequate composition of blood components should be given. Specific blood components should be employed to correct specific deficits.

Other supportive measures are directed to the cardiac and pulmonary status

of the patient, adequate immobilization of the infected and injured part (including fractures), relief of pain, management of renal failure, and treatment of thrombophlebitis (which is a frequent and prominent manifestation of anaerobic infection). The use of anticoagulants should be weighed against the risk of specific hemorrhage.

Patients with gas gangrene run an increased risk of developing tetanus, because tissues with *C. perfringens* are equally suitable for *C. tetani*. Tetanus prophylaxis is necessary, according to the guidelines of the Committee on Infections of the American College of Surgeons.

Before hyperbaric oxygen therapy became available, the treatment of gas gangrene was almost entirely surgical. The main object was to excise or amputate as soon and as generously as possible so as to remove all diseased tissue; even disarticulations were considered. Limb-saving operations were discarded in favor of life-saving procedures directed to radical extirpation of the site of infection. Removal of all compromised tissue was thought to prevent clostridial growth and thus arrest the onset and spread of gas gangrene. Although the mortality decreased, it still remained between 20 and 50%; even when the disease was discovered early, the mortality remained well over 10%. Moreover, patients who lived were often disabled and subjected to long-lasting physical and psychologic rehabilitation programs.

Initially after discovery of the causative anaerobic microorganism, application of hydrogen peroxide and zinc peroxide creams was tried. These efforts changed the Po_2 at the surface and in superficial layers, but not in the center of the infection. Slightly better results were reached after other modalities of local application of oxygen, as follows: (1) allowing oxygen to penetrate the wounded tissues by inserting tubes, or (2) injecting oxygen into the wound and into the tissues at the borderline of a progressing infection. But, still, there were parts of the body (e.g., intra-abdominal and intracranial) that were not suitable for injection therapy. During World War I, German surgeons warned against this injection therapy, which was sometimes complicated by fatal gas embolism.[47] Local oxygen therapy was disappointing and could not be recommended.[18]

In a survey of 607 patients with gas gangrene treated with all kinds and combinations of treatment modalities, the mean mortality was 49.7% (range, 19–55%). The patients were treated by incision, drainage, debridement, amputation, disarticulation, serum therapy, rib resections, charcoal therapy, and irrigations with hydrogen peroxide and/or Dakin's solution. In serious cases, 50% mortality is still reported without hyperbaric oxygen therapy.[56] During World War I, the mortality of gas gangrene in the American Expeditionary Force in France was 48.5% (674/1389 patients with gas gangrene).[35] Today's treatment for gas gangrene includes surgery, antibiotics, general resuscitative and ancillary measures, and hyperbaric oxygen.

Surgery

Surgery has an important place in gas gangrene, but it has undergone changes in timing and extent since hyperbaric oxygen became available. In clostridial cellulitis, it is, in general, sufficient to perform large incisions and, if necessary (because of tissue necrosis), excisions only as deep as the deep muscle fascia.

In clostridial myositis and myonecrosis, the main objective is the removal of

dead tissue and blood because erythrocytes, containing catalase, counteract the influence of hyperbaric oxygen. The problem in gas gangrene is not dead or healthy tissue, but is the quickly advancing phlegmon in between the two. This phlegmon of infected, but viable tissue is best treated primarily by hyperbaric oxygen instead of surgery. Initial surgery can be limited to wound opening in traumatic and postoperative patients, and sometimes decompressing fasciotomy; no ablative surgery is necessary, in our experience.

In most cases, removal of necrotic tissue can be delayed until after the fourth hyperbaric oxygen session or even until hyperbaric treatment is completed, depending on the general condition of the patient.

Antibiotics

General consensus has been reached as to treatment of the life-threatening clostridial myonecrosis with high doses of antibiotics. Penicillin is preferred, in combination with one or two other antibiotics directed against mixed superinfections.[15,19,20,22,31,42] Chloramphenicol is suggested as a reasonable alternative for patients with severe penicillin allergy, because of the sensitivity of most anaerobes to this drug.[34] The potentially lethal hematologic complications of chloramphenicol prompted many clinicians to use erythromycin, lincomycin, and clindamycin for anaerobic infections in general.[5]

For the treatment of myonecrosis and clostridial cellulitis with toxicity, the best choice after penicillin-G is probably clindamycin, vancomycin, and metronidazole.[14] Clostridia other than *C. perfringens* are less sensitive to clindamycin and vancomycin. In our patients, *C. perfringens* was responsible for gas gangrene in 95.8% of cases. In order to minimize the potassium load in patients already at risk for hyperkalemia, sodium penicillin is proposed for use instead of potassium penicillin, according to the following schedules: 6–20 million units penicillin/day and clindamycin intravenously (in adults, 600 mg/6 hr; in children, 5 mg/kg body weight/6 hr) as well as gentamycin (or tobramycin) (in adults, 1.5 mg/kg body weight/8 hr; in children, 2.5 mg/kg body weight/8 hr, depending upon the renal function). We consider antibiotics as an adjuvant in the treatment of gas gangrene with hyperbaric oxygen.

Hyperbaric Oxygen

The action of hyperbaric oxygen on clostridia and other anaerobes is based on the formation of oxygen free-radicals in the absence of free-radical degrading enzymes, such as superoxide dismutases, catalases, and peroxidases.

The first clinical results in gas gangrene were remarkable but were difficult to reproduce in the animal model.[25,26] This can be explained in part by the fact that pressures used in some of the experiments were too low, because the resistance of small laboratory animals against a high Po_2 is different from that of human beings. Van Unnik[49] showed that a Po_2 of 250 mm Hg is necessary to stop alpha toxin production completely, although this does not kill all *Clostridium welchii*. Hyperbaric oxygen is, however, bacteriostatic and bactericidal for *Clostridium welchii*.[25,26] Local application of oxygen is of no use in the treatment of gas gangrene. Nora et al[38] showed that hyperbaric oxygen at 3 atmospheres absolute pressure (ATA) had no effect on cell-free, preformed alpha toxin.

Animal experiments and clinical data show that a combination of hyperbaric oxygen, local debridement, and antibiotics led to less mortality and morbidity than any of these treatment modalities alone.[19,20,28]

It is very important that hyperbaric oxygen therapy start as early as possible, because the best treatment results are achieved in the earliest possible stage of the infection.[22] Results worsen progressively when hyperbaric oxygen treatment is delayed. Early and aggressive surgery and late hyperbaric oxygen treatment lead to a significantly higher mortality and morbidity.[46] The performance of time-consuming procedures before hyperbaric oxygen treatments is contraindicated, since it further endangers the life of the patient. In our experience, it was nearly always possible to delay more definitive surgery until hyperbaric oxygen treatment for gas gangrene had been completed. The advantages of early hyperbaric oxygen treatment are that:

1. It is *life-saving* because less heroic surgery needs to be performed in very ill patients, and the cessation of alpha toxin production is rapid.
2. It is *limb- and tissue-saving* because no major amputations or excisions are done in advance, and, when demarcation becomes clear, far less tissue appears to be lost than initially thought.
3. It *clarifies the demarcation*, so that there is a clear distinction between dead and still-living tissue within 24–30 hours.[4]

Advocated pressures vary from 2.5 ATA in a monoplace chamber to 3.0 ATA in a large multiplace chamber during 90 minutes of 100% O_2 breathing per treatment session. Frequency of treatment varies from three to four times during the first 24–28 hours up to a total of seven treatments, to continuation of two treatments daily after 48 hours until the infection is completely controlled. We have never used more than seven treatments in 3 days. During this time, infection was controlled or the patient died. As soon as the patient is breathing 100% O_2 at the required pressure, the tissue Po_2 around and even inside the infected area rises to values over 250 mm Hg, so that the production of alpha toxin stops completely.[45] Within 30 minutes the circulating toxin is fixed to the living cells,[31] and the growth of clostridia is limited. After a short interval, the hemolytic tissue-necrotizing and lethal activity of the clostridia is stopped.

Between hyperbaric oxygen sessions when the patient is at sea level pressure, alpha toxin production starts again, but, before a dangerous level is reached, the next session stops production once more. The intermittent periods without alpha toxin production and the rapid destruction of circulating alpha toxin enable the body to utilize its own host defense mechanisms. The temporary arrest of alpha toxin production may lead to a change in the environment of the clostridia, which consequently no longer meets the requirements for optimum function of the clostridia. The transiently increased pH, the arrest of the activity of proteolytic enzymes in the tissue, and the consequent arrest of the release of amino acids in the lesion may result in a condition of the surrounding tissues that is not ideal for the functioning and multiplication of anaerobic microorganisms. In the infected area, the circulation is improved by diminished edema and compression of gas bubbles. It goes without saying that already necrotic tissue is lost, but the quantity of tissue to be lost is, in our experience, always far less than that initially expected before hyperbaric oxygen treatment.

AMSTERDAM THERAPEUTIC REGIMEN

Before a patient suspected of gas gangrene is transferred to the hyperbaric unit, colleagues from the referring hospital are advised to transport the patient to the unit without delay and, in the meantime, to refrain from surgical intervention and to treat the patient with 1–2 million units penicillin-G intravenously.

Thereafter, in our unit the following protocol is carried out:

1. Wound inspection to evaluate the clinical picture, discoloration of skin, muscle necrosis, swelling of the infected area, discharge and smell from the wound, in order to ascertain whether gas gangrene is involved.
2. Removal of sutures and opening of the wound is performed in sutured postoperative or posttraumatic wounds. In cases of gas gangrene after injections or minor injuries, wounds are not surgically handled (i.e., no incision or excision).
3. Bacteriology, including a direct smear for Gram stain, aerobic and anaerobic blood and wound cultures, and tissue specimens for histology. A Gram stain with gram positive clostridial rods supports the clinical diagnosis of gas gangrene, and hyperbaric oxygen treatment is indicated. However, before the results of cultures are known, treatment is started because the alpha toxin production has to be stopped as quickly as possible.
4. Demarcation of the boundaries of discoloration and crepitance.
5. Blood sampling for laboratory investigation, including hemoglobin, hematocrit, leukocytes, electrolytes, kidney and liver function tests, arterial blood gases, etc.
6. Infusion therapy and treatment for shock as soon as the patient arrives in the hospital.
7. X-rays for signs of clostridial myositis.
8. Antibiotics (6 × 1 million units penicillin-G/day).
9. Chloral hydrate as a sedative (1 g rectally), which has proved to be useful and relatively harmless. Interaction of other sedatives and their use under hyperbaric conditions have been outlined by the Undersea Medical Society.[52]
10. Myringotomy performed in patients (small children, very old, and seriously ill patients) who are not capable of "clearing the ears," to equalize the difference in pressure on both sides of the eardrum during treatment. Myringotomy is easily and quickly performed under local anesthesia and is virtually without complications. The opening in the eardrum remains competent during the 3 days of treatment. If, for other reasons, treatment with hyperbaric oxygen has to be continued, tympanostomy tubes are inserted.

Results

Between October 1960 and December 1985, 547 patients suspected of gas gangrene were admitted to our department. In 409 cases (72.9%), the diagnosis of gas gangrene could be confirmed both clinically and bacteriologically. Bacteriologic confirmation of blood and/or wound cultures for at least one pathogenic *Clostridium* species invariably followed the first 24 hours of hyperbaric oxygen therapy. A positive clinical picture and a Gram stained smear with gram positive spore-bear-

ing rods and without leukocytes were arguments to start treatment forthwith. The lack of initial bacteriologic confirmation of the diagnosis of gas gangrene should not delay treatment in cases of clinical gas gangrene.

Sex and Age Distribution

The group of 409 patients with proved gas gangrene consisted of 309 men (75.5%) and 100 women (23.5%), with a mean age of 44.4 years (range, 5–94 years).

Classification of Patients with Gas Gangrene

Our patients were classified into three groups according to the cause of gas gangrene: Group I (n = 257), accidents; Group II (n = 124), operations; and Group III (n = 28), other causes. The majority in Group I acquired gas gangrene after a traffic accident (n = 185); in second place were industrial or agricultural accidents (n = 37). Only in six cases were sports accidents involved. Finally, in 29 cases, gas gangrene was caused by another kind of accident.

In Group II, 124 patients acquired gas gangrene postoperatively, either after acute or after elective surgery. Every operation can be complicated by gas gangrene. A sudden rise in temperature within the first 24 hours after operation, together with the onset of disproportional wound pain, may be a sign of gas gangrene, even after the most elective and "sterile" operation (Table 7.1). Most patients (n = 61) developed gas gangrene after amputation for arteriosclerotic and/or diabetic gangrene. As a result of seriously impaired circulation, these patients already suffer from tissue ischemia or necrosis, which are important factors in the etiology of gas gangrene.

A clear distinction should be made between the so-called infected vascular gangrene (nontraumatic histotoxic infection) and true gas gangrene. Infected vascular gangrene is, in general, a much more chronic, relatively benign infection without symptoms of general toxicity. The patient is not very ill, has no high fever, and the soft tissue infection without myonecrosis is located in the amputation stump. Clostridia can be present in this mixed aerobic-anaerobic infection. The slight degree of myositis or myonecrosis usually has an appearance different from that of true clostridial myonecrosis and runs a course different as well. Only clostridial myonecrosis in a seriously ill patient with a fulminant progressive disease involves gas gangrene and needs hyperbaric oxygen treatment.

In view of the possible endogenic source of clostridial spores, there is a slight prevalence of gas gangrene after surgery of the colon (n = 9), gallbladder (n = 9), perineum (n = 5), and for ileus (n = 6). The third group (n = 28) is probably the most difficult, but also the most interesting, category; it has a variety of causes (Table 7.2), of which intramuscular injections take the greatest part (n = 8). It is clear that clostridial growth may be expected in areas of ischemia caused by an injected substance with a vasoconstrictive effect, e.g., epinephrine. In one case of intravenous (IV) infusion, gas gangrene developed 1½ hours after venipuncture. Two exceptional cases of gas gangrene occurred after an insect sting while the patients were gardening.

TABLE 7.1 Type of Operation Preceding Gas Gangrene[a] and Mortality Due to Gas Gangrene[b]

Type of Operation	No.	Mortality
Amputation for arteriosclerotic and/or diabetic gangrene	61	9
Colonic surgery and trauma	9	3
Cholecystectomy	9	3
Sympathectomy	6	—
Perineal abscess and wound	5	—
Ileus	6	3
Osteosynthesis (not acute)	3	1
Amputation (after trauma)	3	—
Appendectomy	3	2
Gastric surgery	2	—
Radical mastectomy	2	—
Arthrotomy knee joint	2	—
Varicectomy	1	—
Prostatectomy	1	—
Herniotomy	2	—
Mitral commissurotomy	1	—
Caesarian section	1	—
Pyelotomy	1	—
Pacemaker implantation	1	—
Embolectomy	1	1
Vascular surgery (no trauma)	1	—
Liver/kidney biopsy	1	—
Arthrotomy ankle joint	1	—
Nonclostridial intracranial abscess drainage	1	—

[a]N = 124.
[b]N = 22.

TABLE 7.2 Kind of Incident Preceding Gas Gangrene in Group III Patients[a] and Mortality Due to Gas Gangrene[b]

Causative Incident	No.	Mortality
Intramuscular injection	8	3
Criminal abortion	3	—
Knee-joint puncture	3	—
Intravenous infusion	3	—
Bladder catheterization	1	—
Ulcus cruris	1	—
Insect sting	2	1
Cowhorn	1	—
Pancreatitis, acute	1	1
No port of entry	5	3

[a]N = 28.
[b]N = 8.

Bacteriology

Clostridium perfringens was the major representative, either in pure culture (357/409, 87.3%) or in combination with other pathogenic clostridia (35/409, 8.6%) (Table 7.3). In 91.2% of cases (373/409), only one *Clostridium* species was cultured. Results of blood cultures could be found in the records of 389 patients. Positive blood cultures were found in 102 cases (26.2%).

Mortality

In order to gain clear insight into the results of hyperbaric oxygen therapy and the survival of patients, it is important to make a distinction between two categories in considering mortality. The first category concerns patients who actually die from gas gangrene during the active phase of the disease and have positive cultures, and the second category involves those who die from other causes after gas gangrene is considered cured. Even in this latter group with cured gas gangrene, it is possible to find positive cultures that can possibly be explained by the difference between the full bacterial life of clostridia with toxin production and the somehow restricted life of clostridia that are still living but not capable of toxin production after hyperbaric oxygen treatment.

In our series, 361 patients survived during the active phase of the disease (mortality 48/409, 11.7%), and 325 ultimately survived. Thirty-six patients died from causes other than gas gangrene (pulmonary embolism, cardiac infarction, metastatic colonic carcinoma, etc.) 4 or more days after therapy. Mortality for the three groups of patients is shown in Table 7.4. In group I, gas gangrene was mainly

TABLE 7.3 Distribution and Type(s) of Clostridia Found in Wound Cultures[a]

Type	Patients
C. perfringens	357
C. septicum	7
C. bifermentans	3
C. sporogenes	3
C. fallax	2
C. novyi	1
C. perfringens + *C. sporogenes*	12
C. perfringens + *C. sordellii*	8
C. perfringens + *C. sphenoides*	4
C. perfringens + *C. bifermentans*	3
C. perfringens + *C. tertium*	2
C. perfringens + *C. novyi*	2
C. perfringens + *C. fallax*	1
C. perfringens + *C. septicum*	1
C. septicum + *C. sphenoides*	1
C. perfringens + *C. sporogenes* + *C. sphenoides*	1
C. perfringens + *C. septicum* + *C. novyi* + *C. sordellii*	1

[a]N = 409.

TABLE 7.4 Mortality of Gas Gangrene for Groups I–III from October 1960 through December 1985

Group	No. Patients	Mortality		
		Overall	Manifest Gas Gangrene	After Full Treatment
I	257	29 (11.3%)	18 (7.0%)	11 (4.3%)
II	124	39 (31.5%)	22 (17.7%)	17 (13.7%)
III	28	16 (57.1%)	8 (28.6%)	8 (28.6%)
Total	409	84 (20.5%)	48 (11.7%)	36 (8.8%)

located in the extremities and was diagnosed at a rather early stage. In Group II, the infection was, in general, located on the trunk or proximal on the extremity. In Group III, the high mortality (8/28, 28.6%) was caused by late diagnosis. These patients were admitted in an advanced stage of infection—septic shock—and consequently could not stand the first 24 hours of therapy.

Figure 7.5 shows mortality in relation to the number of hyperbaric sessions. If patients survived until the fourth hyperbaric session (which started 24 hours after the first treatment), there was no more mortality from gas gangrene. All 48 patients

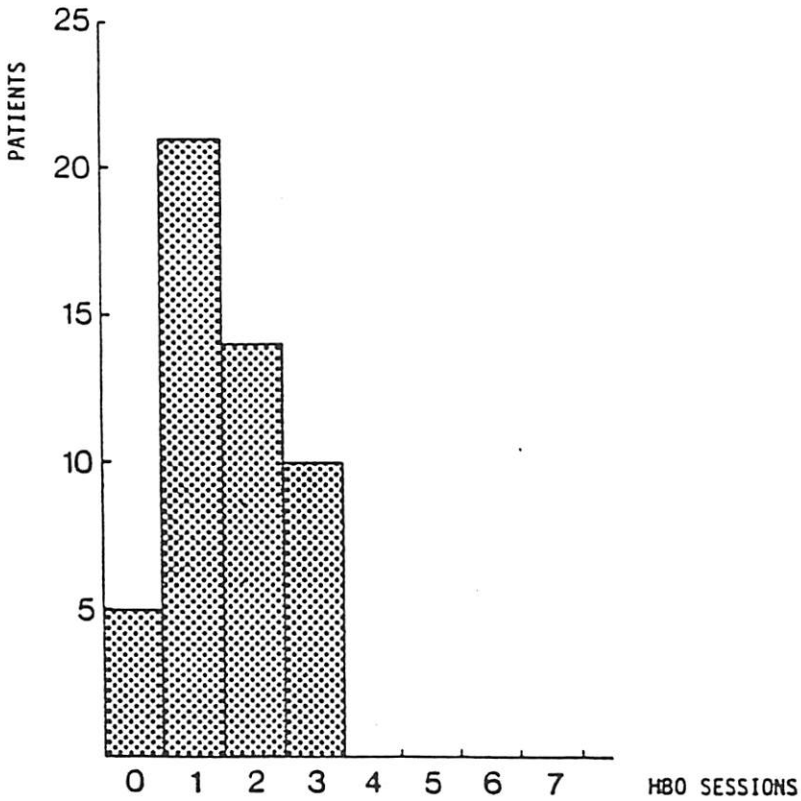

FIGURE 7.5 Mortality from manifest gas gangrene (48/409) during hyperbaric oxygen therapy (October 1960 through December 1985).

died within 24 hours after the start of hyperbaric oxygen therapy, before the fourth session. It is hardly possible to show more clearly than in the Figure 7.5 how important time is in the treatment of gas gangrene.

Amputations

Between October 1960 and December 1985, the total number of patients with gas gangrene of the extremities was 311. Eighty-one patients had already undergone amputations elsewhere for arteriosclerotic and/or diabetic vascular insufficiency (61), gas gangrene (14), or trauma (6). Amputations for gas gangrene (14/311, 4.5%) were mostly performed between 1960 and 1965. During that period, surgeons were not acquainted with the fact that primary surgery was not necessary if hyperbaric oxygen facilities were available; between 1975 and 1985, only two amputations for gas gangrene were performed before sending the patient to us.

After completion of hyperbaric oxygen therapy, 56 amputations were necessary (56/230, 24.3%), reamputation or stump correction was carried out 15 times in primary amputated patients (15/56, 26.8%), and in 21 cases ablation should be called extensive debridement. In all of these 21 patients, the extremity was already considered to be lost because of frank necrosis at the time of admission, although amputation had not been carried out at that time. In the other 20 cases (20/230, 8.7%), amputation had to be carried out despite hyperbaric oxygen therapy. This clearly demonstrates a lower amputation rate than that after primary surgery, reported to be 50–55%.[46] Based on these results, we postulate that primary ablative surgery to treat gas gangrene of the extremities is contraindicated.

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