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Gas Gangrene—Clostridial Myonecrosis: A Review

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Introduction

Botini (1) demonstrated the bacterial nature of gas gangrene in 1871 but failed to isolate a causal organism. The first description of "gas gangrene" with accurate clinical, bacteriologic, and pathologic observations was made by Welch and Nuttall (2) in 1892. This was further expanded by Welch's later report (3) in 1900. Gas gangrene is herein defined as that fulminate necrotizing infection caused by Clostridia and may or may not have gas in the involved tissues. The most frequent species of Clostridia causing gas gangrene was first designated *Clostridium welchii* following the aforementioned publications. However, at present this species is known as *C. perfringens* and is generally accepted as being the most common and virulent form of gas gangrene.

Etiology

Gas gangrene is classically and mistakenly almost exclusively associated with trauma. Recent reviews indicate that 50% of the cases arise from the contamination in trauma wounds while the remainder occurs after surgical procedures not involving trauma and arising spontaneously (no injury, no surgery) (4-8). The apparent mix at the present time is probably 49% from posttraumatic causes and the remainder from postoperative (35%) and spontaneous (16%) causes.

Bacteriology

Louis Pasteur first isolated and described *C. butyricum* in 1861, and 150 species have been isolated since that time. Clostridia are putrefactive, Gram-positive anaerobic, spore-forming encapsulated bacilli, which are motile or nonmotile, depending on the species. Most are soil contaminants. They have been isolated from the stomach, gallbladder, small bowel, colon, vagina, and skin in healthy individuals (9, 10).

Clostridium perfringens has been implicated either alone or in combination with other organisms in 50-100% of all gas gangrene infections (11-14). Further, *C. perfringens* may multiply at normal tissue PO_2 (15). The clostridial species reported as causative agents occur in 3 distinct groups and are listed

in Table 1. Group I includes the species that cause the classical syndrome of gas gangrene. They possess toxigenic and proteolytic capabilities. In group II are those that are not toxigenic but augment an infection by their proteolytic capabilities. The clostridial species in group III are believed to be wound contaminants only.

Pathogenesis

Clostridia thrive in tissues with low oxygen tension. When tissue is damaged, its vascular supply may be compromised and the tissue oxygen tensions lowered. If the tissue is contaminated with clostridia, the organisms then have an ideal environment in which to multiply. Exotoxins are released, beginning the fulminant phase of the infection which progresses to an intense edema around the area of necrosis with little or no inflammatory response. This further compromises the available blood supply, reducing the availability of white blood cells (WBCs) while lowering further the oxygen tension in the involved tissues. This sequence leads to the rapid spread of the necrotizing process. The patient may become moribund in 12 h, and death secondary to fulminating toxemia has been reported as quickly as 12 h (16).

Five major and four minor exotoxins of *Clostridium perfringens* are responsible for changes seen locally and systemically in the affected patient (15). The alpha toxin, a C-lecithinase, is the major lethal toxin. It causes hemolysis, necrosis, and is oxygen stable, i.e., remains active when exposed to HBO at 2-3 atm abs (17, 18). The hemolysis leads to anemia, hemoglobinuria, jaundice, oliguria, and often to renal failure (16, 19). The remainder of the exotoxins assist in destroying, liquefying, and dissecting into the adjacent healthy tissues, producing the fulminant and rapid spread of the infection. The proteolytic and saccharolytic enzymes produce hydrogen sulfide (20). Pathogenesis is not simply limited to "local tissue destruction" but involves profound histochemical effects on the kidney, heart, and brain by the soluble exotoxins (15, 21). Notably, the theta toxin that is cardiotoxic is oxygen labile and neutralized by oxygen (15). Other histotoxic clostridia liberate their own specific exotox-

Table 1: Clostridial Species Causing or Associated with Gas Gangrene

Toxigenic & Proteolytic, Group I	Proteolytic, Group II	Contaminant, Group III
<i>Perfringens</i>	<i>bistolyticum</i>	<i>tertium</i>
<i>Septicum</i>	<i>bifermentans</i>	<i>busyricum</i>
<i>Nouyi (oedematiens)</i>	<i>sporogenes</i>	<i>paraputrificum</i>
	<i>fallax</i>	<i>sartagoforum</i>
		<i>sordellii</i>
		<i>capitovales</i>

ins, such as the alpha toxin of *C. novyi* (otherwise known as *C. oedematiens*) which affects vascular permeability so that edema is the predominant presentation producing little or no gas (22).

Incidence

The greatest mortality recorded in the medical literature from gas gangrene was during World War I when 10–12% of the wounded died from gas gangrene (23). Altemeier and Furste (11) reviewed 187,936 major open wounds and found the incidence of gas gangrene to be 0.03–5.2%, depending on the type of wound and the treatment. Smith et al. (24) report the incidence of criminal postarboral clostridial gangrene to be 0.5–1.0% (24). Parker (4) reports 56 cases of gas gangrene occurring in clean, elective, postoperative patients over a 2-yr period in 55 British hospitals. These figures would indicate that U.S. hospitals could have over 1000 cases of gas gangrene per year in clean, elective surgical patients. If the preceding represent 35% of the cases as reported in the past 3 decades (6, 7), then the annual estimate for the United States would be over 3000 cases per year.

Diagnosis

Early diagnosis is the most crucial part of successfully managing gas gangrene. The classically described picture of an edematous wound with bronze, grey, or purplish discoloration, a brown, watery discharge, hemorrhagic bullae, a rapidly extending margin of erythema, and palpable crepitation is a *late* finding (25). Early signs of infection include subtle changes such as progressive, disproportionate increase in wound or incisional pain, a tachycardia not in proportion to fever, mental changes reflected by apathy or indifference, and/or shiny skin about a wound indicating early edema. Progression from these changes toward the classic description indicates advancing disease. A high index of suspicion must be maintained in any situation where the patient may be compromised by hypotension, vascular impairment, edema, tight retention sutures, tight casts, and abdominal distention (26, 27). Diagnosis, early or late, is made by the clinical assessment (27).

A Gram-stain of wound drainage is the most rapid proven laboratory means of confirming the suspected diagnosis of gas gangrene. The presence of Gram-positive bacilli in the presence of the subtle or late wound changes listed above should be considered gas gangrene until proven otherwise (25). Treatment must be initiated before cultures are available because anaerobic cultures usually require 48 hours to complete inasmuch as Clostridia are fastidious organisms, often requiring 48–72 h for growth in culture media. Changes in WBC count, bilirubin, and renal function measurements are late signs and may be helpful prognostic yardsticks but not early diagnostic aids (8, 25, 28).

Importantly, radiographs will not consistently reveal gas in the early phase of the infection and the presence of gas is not pathognomonic for clostridial

gas gangrene (29, 30). This is particularly important when the clostridial myonecrosis is the so-called wet type caused by *C. novyi (oedematiens)* which produces little or no gas even in the late phase of the disease. When gas does occur in the wounds and appears in a feathery pattern indicating dissection along the muscle fascicles, rather than in large bubbles, the diagnosis of myonecrosis should be entertained, except for the soft-tissue gas patterns associated with open wounds or necrotizing fasciitis.

A new assay (31), yet to be proven in the human, that can be obtained on tissue fluid or tissues within 8–12 h after the onset of the clostridial infection seems promising in establishing the diagnosis of gas gangrene. Table 2 is the authors' modification of a classification popularized by Altemeier and Fullen (25).

Classifications such as the preceding have been used as algorithms for initiating treatment in gas gangrene. We are convinced that categories I, II, and IIIa should be managed by a combination of surgery, antibiotics, and hyperbaric oxygen (HBO) in a timely, aggressive fashion; IIIa is included as it may rapidly progress to levels I or II if not managed appropriately (5).

Differential Diagnosis

The combination of gas in the tissues and a necrotizing myositis does not always indicate a clostridial infection. However, to salvage life or limb it is imperative that radical treatment be instituted within the first 24 h of onset (25). The differential diagnosis is shown in Table 3, which is a modification of the data presented by Bessman and Wagner (29) as reflected by our experience.

A careful history and physical examination are the primary methods in differentiating the causes of gas gangrene (20, 25, 29, 32). Notably, extensive gas in the soft tissues with an absence of toxicity suggests a gas-forming fasciitis usually of an aerobic nature or from accidental or purposeful gas injections. Example: A metal lathe worker was emergently transferred with gas gangrene, having attempted to blow metal filings from a small laceration on the forearm

Table 2: Classification of Clostridial Infections

Category and Type	Subtype	Examples
I Clostridial myonecrosis	a. Spreading crepitant b. Diffuse or noncrepitant	
II Primary organ		Uterus, gallbladder
III Clostridial cellulitis	a. Anaerobic toxemia b. Localized	
IV Clostridial contamination		

Table 3: Differential Diagnosis of Soft-Tissue Gas

Bacterial

- I Aerobic aerogenic infections
 - A. Hemolytic staphylococcal fasciitis
 - B. Hemolytic streptococcal gangrene
 - C. Coliform
- II Anaerobic streptococcal and staphylococcal infections
- III Bacteroides infections
- IV Clostridia
- V Mixed aerobic and anaerobic infections
 - A. Combined synergistic bacterial gangrene
 - B. Meleney's ulcerations
 - C. Fournier's gangrene
- VI *Bacillus cereus* infection. A difficult differentiation that will require days and sometimes weeks to discern from clostridial infections.

Nonbacterial

- I Mechanical injection of gas
 - A. Mechanical effect of trauma
 - B. Air hose injury
 - C. Drug addict air injection to mimic gas gangrene
- II Chemical injection
 - A. Hydrogen peroxide irrigation
 - B. Benzine injection
- III Postoperative
- IV Barotrauma/dysbarism
- V Aberrant sexual activity

insufflating the entire extremity to such a degree that the gas dissected onto the chest wall. A Gram-stain of fluids or tissues is helpful in providing immediate identification of the organism or organisms present. Tissues submitted for frozen section in clostridial infection will reveal a necrotizing, nonsuppurative infection. Suppurative infections such as streptococcal myositis will reveal inflammatory and polymorphonuclear cell infiltration in the tissues.

Gas gangrene occurring "spontaneously" and culturing *C. septicum* must be carefully investigated as it may have metastasized locally or distantly from the penetration of a gastrointestinal malignancy. Example: A 24-yr-old female in shock, with necrotizing infection of the left flank just above the iliac crest, was treated energetically with HBO, surgery, and antibiotics. *Clostridium septicum* was cultured. Recovering from the infection, a history of a change in bowel habits and weight loss was elicited, and contrast studies revealed an extensive neoplasm of the colon. She succumbed to the malignancy (adenocarcinoma) within the year. Two others had "spontaneous" clostridial infections from gastrointestinal tract carcinomas, recovered from the infection only

to die within months from the underlying neoplastic process. Five patients have had spontaneous clostridial myonecrosis with leukemia or lymphomas. Only 1 patient, of these 8, survived a year after the infection and he had chronic myelogenous leukemia. Therefore, one must include malignancy as a cause of gas gangrene as noted by Nordkild and Crone (33). The absence of gas in the wound does not exclude gas gangrene from the diagnostic possibilities. Example: A 17-yr-old male stepped on a sharp object in a barnyard, penetrating the sole of the shoe and into the plantar aspect of the foot. He experienced the rapid onset of a necrotizing infection with swelling of the foot, ankle, and calf. No gas was found in the extremity and C. *novyi* (oedematiens) was cultured from debrided tissues. He required a partial forefoot amputation, antibiotics, and HBO to cure the infection.

Treatment

Surgery and antibiotics remain the cornerstones of treating clostridial myonecrosis, but hyperbaric oxygen has proven to be a valuable adjunct (34-37). The effectiveness of serum therapy (antitoxin) has not been proven and the serum side effects do not justify its use (27). Debridement alone has not been found to lower the morbidity and mortality after the infection is established. Antibiotics alone will not prevent gas gangrene in the absence of an adequately debrided wound (16, 20, 25, 26, 38-41).

Surgery

The standard of surgical care of gas gangrene has not changed since reported by Wilensky (42) in 1918. His tenets regarding surgery remain valid today as follows:

1. The opening up completely of the entire wound including all pockets
2. The removal of all dirt and the mechanical cleansing of the wound
3. The removal of all foreign bodies
4. The eradication of all haematoma, small and large
5. The removal of all muscle tissue which is in anyway compromised
6. Complete hemostasis
7. It is imperative to institute wide and abundant drainage.

Wilensky may not have understood the pathophysiology or bacteriology involved in these dicta for debridement but they have withstood the scrutiny of modern science; for example, the necessity of establishing hemostasis and removing hematoma. Disintegrating erythrocytes release catalase. The catalase is then used by the anaerobes remaining in the wound to metabolize the peroxides formed within the bacteria (43). Surgical debridement remains an essential component of the combined therapy of gas gangrene. Comparison of mortality and morbidity from gas gangrene between World War I and World War II shows a marked reduction in rates in the latter conflict. This is attributed to timely surgery performed in

medical units positioned close to the action and the use of antibiotics in the later stages of World War II. The further reduction in incidence and mortality in more recent conflicts (Korea and Viet Nam) is attributed to the expeditious use of helicopters in casualty evacuation to military medical units and the use of preventive measures such as penicillin prophylaxis combined with surgical techniques such as early debridement and delayed primary closure (41, 44).

We presently, *conservatively*, debride only the obviously necrotic tissues and leave the involved area open. The patient is placed on the critical care unit if constant monitoring is required, otherwise he or she is placed in the wound management ward. The wounds are treated aggressively by dressing changes four times daily with a wet-to-dry technique using a physiologic saline solution such as Ringer's irrigation. Debridements and amputations are performed as indicated by the level of viability.

Antibiotics

Antibiotics comprise the second essential component in the combined therapy for gas gangrene. The reduced morbidity and mortality of wounds in the penicillin era were verified in animal studies by Irvin et al. (45) and Demello et al. (34). Penicillin is the drug of choice, since its introduction during World War II, for prophylaxis and treatment of gas gangrene (16, 25, 26, 38, 46). No antibiotic yet studied has proven superior to penicillin. The sodium salt of penicillin is recommended rather than the potassium salt because the latter will increase the hyperkalemia that may be present secondary to hemolysis, tissue destruction, and renal failure. Penicillin dosages of 10 to 24 million units per day are recommended (27, 47, 48). Inasmuch as only 10–15% of patients with a history of penicillin allergy are truly allergic to this antibiotic, sensitivity testing for those with a penicillin allergy history is recommended because of its proven effectiveness. In the presence of penicillin allergy, tetracycline is recommended as an alternative (dosage, 2–4 g i.v. per day) (26, 27, 40). In vitro testing has revealed the existence of strains resistant to tetracycline (49). Chloramphenicol, in high doses, and erythromycin and clindamycin have also been recommended (28, 39, 50). Keflin has been reportedly effective in high doses (6–12 g i.v. per day) (35). However, Keflin does not seem to be a satisfactory prophylaxis at 2–6 g i.v. per day because Mohr and associates (51) report four cases of gas gangrene occurring in patients with compound fractures receiving this regimen. Imipenem has been found effective against penicillin-resistant murine strains of *C. perfringens* (52).

Hyperbaric Oxygen

Adjunctive HBO is recommended at pressures sufficient to elevate the tissue O_2 to greater than 250 mmHg to be bacteriostatic and to stop the elaboration of the exotoxins (53, 54). HBO at 3 atm abs has been shown to raise tissue O_2 pressure above 300 mmHg (55–60). The aforementioned animal studies have

been replicated (61–63) by one device or other in the human in tissues other than the central nervous system tissues.

Since 1960, when Brummelkamp et al. (64) reported the successful treatment of gas gangrene with adjunctive HBO at 3 atm abs, HBO has been a component of therapy for gas gangrene. Controversy was generated with this new modality when Roding et al. (65) reported that antibiotics and surgery were not necessary if HBO treatment was begun early in the clostridial infection.

Both bactericidal effects in vitro and bacteriostatic effects in vivo on clostridia using HBO are reported (66–68). Irvin and associates, in animal studies, note that HBO is not sufficient as a sole therapeutic entity and in fact later suggest that it has no use at all (9, 45, 69). Demello and colleagues (34) compared combinations of surgical debridement, antibiotics, and HBO in a dog model in 1973. A superior survival rate (95%) was achieved by a combination of surgery, antibiotics, and HBO when compared to surgery and antibiotics (70%), surgery alone (0%), and HBO alone (0%). Antibiotics alone resulted in a 50% survival rate. Holland et al. (35) report that exposure to HBO in the first 48 h of gas gangrene infection in mice significantly reduced mortality ($P < 0.001$). These basic in vivo studies note a reduction in mortality in animal models in the peer-reviewed English literature and clearly delineate the application of HBO as an adjunct to antibiotics and surgery in attending gas gangrene.

The risks of HBO have been emphasized in the literature and include oxygen toxicity, barotrauma, decompression sickness, damage to the lungs, and fire (16, 20, 70). The frequency of complications related to HBO is low (71) and the unit at our facility has over 100,000 patient compressions without a chamber-related death. Further, should CNS oxygen toxicity become apparent, HBO may be continued if anticonvulsant therapy is instituted (72). A report indicates a remarkably high incidence of oxygen toxicity by including symptoms, such as anxiety reactions, that are interpreted as "suggestive of oxygen toxicity" (73). We find that all rational patients have some degree of confinement anxiety in response to the confines of a hyperbaric chamber and some have a certain anticipation anxiety due to the obvious magnitude of the infection. These anxieties are allayed by properly trained and experienced medical and nursing personnel. The treatment protocols presently available and with proper attention to avoiding those drugs that accelerate oxygen toxicity will reduce oxygen toxicity to an acceptable level.

Several recommended successful HBO protocols range from pressures of 3.0 to 2.0 atm abs and exposure times of 90 min with 100% oxygen to 5–12 h breathing oxygen intermittently with periodic air breaks (5, 8, 16, 74, 75). We have favored the following protocol for monoplace chamber application: HBO pressures of 2.5 atm abs oxygen 90 min 3 times a day during the active phase of the infection. It is well tolerated in terms of side effects and adequate for HBO to be effective. The treatments are decreased to 90 min 2.5 atm abs

oxygen twice a day during the second 24 h and continued until there is no evidence of toxicity from the alpha toxin (hemolysis).

The perennial argument is when do you apply HBO: before or after surgery? The policy in our department is as follows:

1. Surgery may be performed first if access to same is within the hour or transfer to the nearest HBO chamber will exceed an hour.
2. HBO is preferred as the first election of the senior author for the following reasons:

- It is rare that the patient will be prepared for surgery within an hour. Type and cross match alone will consume this amount of time. Gaining access to an operating suite in a busy medical center will require this amount of time.
- HBO will stop the elaboration of the alpha toxin and the proliferation of the organisms. It will neutralize the theta toxin.
- Antibiotic levels may be maximized during the HBO treatment.

One of the major benefits of HBO is inhibition of toxin production (53). Alpha toxin of *C. perfringens* already produced at the time of HBO exposure is stable in the hyperoxygenated tissues, but other toxins such as the theta toxin are inactivated (14, 66). HBO at 3 atm abs has been reported to be bactericidal to some strains of clostridia in vitro while being bacteriostatic when the same pressures are applied in vivo (66, 67, 76). An important role of HBO is to counteract the hypoxic environment in which the clostridia thrive while peroxides develop within the organism to inactivate or kill the clostridia. The presence of catalase in muscle and blood may be used by the clostridia to inactivate the peroxides (43). Hence, surgery complements the effects of HBO by removing the necrotic tissue and red blood cells which may release catalase. *Clostridium perfringens* stops producing toxins in ambient oxygen tensions of 80 mmHg or greater, whereas a pressure of greater than 200 mmHg is required to stop replication. Normal tissue partial pressure of oxygen (P_{rO_2}) while breathing air is 30–40 mmHg. P_{rO_2} of 250 mmHg at 2 atm abs O_2 to 450 mmHg at 3 atm abs O_2 are achieved with HBO (Table 4) (56, 57, 61).

The improved results of the past 3 decades reflect survival rates of 90–100% from gas gangrene arising after trauma of the extremities treated with HBO, antibiotics, and surgery (35, 36, 77–81). Most historic controls without HBO

Table 4: Effects of HBO In Vivo on Clostridial Infections

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1. Bacteriostatic at pressures tolerated by man.
 2. A tissue partial pressure of oxygen greater than 200 mmHg is required to stop the elaboration of exotoxins.
 3. Intermittently relieves the hypoxia of surrounding ischemic tissues.
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display an overall mortality rate above 40% (35, 82, 83). The last statement is amplified by Bakker (84) (Tables 5 and 6).

Altemeier and Fullen's (25) is the only report in the literature in the past 20 yr noting an extremely low mortality rate (14.8% in 54 cases) using only radical surgical debridement and antibiotics. This report appears, however, to deal with posttraumatic extremity gas gangrene, where very radical surgery was performed in the first 24 h of the infection and thus misleads the casual observer. Where the statistics are available, the combination of HBO, antibiotics, and surgery is superior to Altemeier and Fullen's report (7 vs. 14.8%). We believe that the treatment of this disease without HBO under the best of

Table 5: Survival of Patients Treated with Combined Surgery, Antibiotics, and HBO

Author	Patients	Survived(%)	Arrived in Shock(%)	Died(%)
Roding (65), 1972	130	101(78)	14(11)	29(22)
Hitchcock (82), 1975	133	100(75)	?	33(25)
Hart (78), 1983	139	112(81)	67(48)	27(19)
Darke (79), 1977	66	46(70)	?	20(30)
Holland (35), 1975	49	36(73)	?	13(27)
Unsworth (85), 1984	53	46(87)	?	7(13)
Hirn (80), 1988	32	23(72)	9(28)	9(28)
Gibson (36), 1986	29	20(70)	?	9(30)
Werry (86), 1986	28	21(75)	?	7(25)
Kofoed (81), 1983	23	20(87)	?	3(13)
Tonjum (77), 1980	14	12(86)	?	2(14)
Total	696	537(78)		159(22)

Table 6: Survival of Gas Gangrene Patients with Only Surgery and Antibiotics

Author	Patients	Survived(%)	Died(%)
Altemeier (25), 1971	54	46(85.2)	8(14.8)
Hitchcock (82), 1975	44	24(55)	20(45)
Gibson (36), 1986	17	5(29)	12(71)
Freischlag (83), 1985	8	3(37)	5(63)
Total	123	78(64)	45(36)

circumstances will result in a mortality rate of 40% or greater and an amputation rate of 50% or greater (Table 7).

The ignorance or misinformation in the use of HBO not infrequently misleads the uninitiated, as it did a former officer who had duty in Viet Nam but had not seen a case of gas gangrene in his 1-yr rotation and came to spurious conclusions (88). Gas gangrene did occur in Viet Nam and the majority of the cases treated successfully were done so with excision of the involved tissues, antibiotics, *and* HBO, as evidenced by the report from the hospital ship, USS *Repose* (89). The casualties afflicted with clostridial myonecrosis were air lifted from medical activities within South Viet Nam to the hospital ship for care because the ship was equipped with a multiplace hyperbaric chamber. The reasons for the unusually low incidence of gas gangrene during this conflict were due to air superiority, which allowed rapid transport to a fully manned and equipped medical facility. The lessons learned during preceding conflicts were aggressively practiced by military surgeons in Viet Nam. The factors relevant to battlefield surgery are covered in the excellent review by MacLennan (14). Further, leaving wounds open for later closure does not save time—it actually costs time and effort and exposes the patient to the risks of a second anesthetic. Military surgeons had an outstanding record in Viet Nam by practicing the lessons learned in prior wars *plus using HBO* when clostridial myonecrosis became apparent in a casualty.

Three reports (90–92) have compared the use of HBO with surgery and antibiotics to that of antibiotics and surgery alone in treating gas gangrene and concluded that the former is superior to the latter. The superiority extends from a mortality of 50–60% without HBO to 20–30% with HBO. The morbidity of amputations are further reduced from 70 to 80% without HBO to below 40%. We noted (78) that amputations required were reduced to 17% in our group compared to past historic controls (50%) which have been recently reviewed by Bakker (87). The report (83) that would encourage a return to the radical surgery of the past is therefore condemned on both medical grounds and the additional, major costs of maintaining amputees.

Table 7: Survival of Posttraumatic Extremity Gas Gangrene Patients with HBO, Antibiotics, and Surgery

Author	Patients	Survived(%)	Died(%)
Bakker (87), 1984	205	191(92.9)	14(7.1)
Hart (78), 1983	58	53(95)	3(5)
Unsworth (85), 1984	53	48(90)	5(10)
Hirn (80), 1988	6	6(100)	0(0)
Werry (86), 1986	8	8(100)	0(0)
Total	330	306(93)	22(7)

The patients in our experience (78) who were retained at the referring institution for a period greater than 30 h after diagnosis by bacterial identification (27 patients), all died. Altemeier's admonition "a 24-hour delay was considered fatal in some patients" was observed in this group, and 23 (85%) of the 27 had third-party coverage. Klopfer et al. (93) noted, significantly, that in an animal model HBO should be applied within a certain time interval to be effective. Sixty-one patients (91%) of the 67 arriving in shock had third-party coverage; the remainder were, to a large extent (70%), dependents on society. Note also that all of the 27 patients received after 30 h had elapsed, died, all received aggressive surgery (most of the amputations [15] had been performed elsewhere in this group) and received appropriate antibiotics before arriving at our treatment facility. Therefore, looking at the delay in treatment of *greater than 30 h as the controls*, we conclude that HBO, if used early, clearly and significantly reduces the mortality of gas gangrene.

Gas gangrene occurring spontaneously in patients due to an underlying malignancy (carcinoma or leukemia) carries a high mortality in our experience: 87.5% within a year of the infection.

Management

We have developed a systematic, efficient approach over the past 20 yr to treating those afflicted with histotoxic clostridial infections. This management algorithm is shown in Table 8.

Diagnosis

Historically, the diagnosis is usually made if an index of suspicion is maintained because of a preceding wound, prior surgery, or the presence of a tumor. The combinations of unusually severe unremitting pain, angry wound margins, watery discharge from wounds, crepitation, rapidly ascending erythema, and/or hemorrhagic bullae should be considered clostridial myonecrosis until proven otherwise. Fever and systemic toxicity may accompany the preceding. The wound with bullae or wound fluid may have a "mousy" or "rotten egg" odor.

Cultures and sensitivities (C&S, both aerobic and anaerobic) should be taken of the wounds. However, at least 48 h will be required to identify these organisms if they are in the inoculating specimen. Thus, institution of an aggressive management routine must be presumptively applied rather than waiting for C&S results. Tissue sections will note a necrotizing infection without purulence where the *Clostridium* is the primary organism, whereas there may be some degree of purulence in mixed infections. The most rapid diagnosis at this time is the Gram-stain of tissues or wound fluids revealing Gram-positive rods, described as boxcarlike in appearance and containing spores. Only one organism can be confused with clostridia on Gram-stain and that is *Bacillus cereus*. The senior author has experienced 2 such cases, with

Table 8: Management of Clostridial Myonecrosis

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- Diagnosis
 - A. History
 - Suspicion
 - Pain
 - Toxicity
 - B. Exam
 - Erythema; edema; watery, mousy odor discharge; hemorrhagic bullae; and crepitation
 - C. Lab
 - Gram-positive rods, evidence of hemolysis
 - D. Radiographic
 - Intramuscular fascicular gas pattern
 - Initial Management
 - A. Antibiotic umbrella
 - Sodium penicillin
 - Aminoglycoside
 - Clindamycin
 - B. Fluids
 - C. Blood
 - Transfer to medical facility with a hyperbaric unit
 - Surgical debridement and initial hyperbaric oxygen therapy
 - A. Invasive monitoring
 - Arterial
 - Swan-Ganz
 - B. Central lines
 - Jugular or subclavian
 - Intense combined management
 - A. Medical (fluids, antibiotics)
 - B. Surgical (wound care, debridements)
 - C. Hyperbaric oxygen
 - Reconstruction/rehabilitation
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survivor in each instance. X-rays may confirm the presence of a characteristic intramuscular fascicular gas pattern in the crepitant patient. A cautionary note, however, is that a species of clostridia, namely *C. novyi (oedematiens)*, forms little or no gas. This organism does cause a large fluid sequestration in the interstitial space and will present a fluid management problem.

Initial Management

Upon entertaining a diagnosis of gas gangrene, medical management is aggressively started using an antibiotic umbrella, without waiting for results of the C&S. Primarily, we use sodium penicillin, an aminoglycoside, and clindamycin. If allergies exist, appropriate substitutes are used. Maximal

doses of each antibiotic are recommended. The sodium salt of penicillin is recommended as these patients are usually hyperkalemic in this necrotizing infection.

Careful attention is essential in maintaining fluid balance because the toxins of these histotoxic organisms interfere with capillary permeability and result in movement of fluids from the intravascular space to the interstitial space, which may be massive and compare to that of an acute burn. Patients in a state of toxic shock must be monitored and buffered for the underlying metabolic acidosis often found in these patients. This is of particular importance because an acidotic state will accelerate oxygen toxicity and may complicate HBO treatments (94). Six to eight units of blood must be available to counteract hemolysis and/or surgical losses of blood. Care must be taken to note hemoglobin concentration due to fluid intravasation into tissue interstices which may disguise anemia.

Transfer to Medical Facility with a Hyperbaric Unit

Transport from one facility to another must be expeditiously completed because delays and interruption of treatment during the transfer will decrease the chances for success (37). Surgery may be done before transfer if this does not further delay the transfer. We recommend the most expeditious transport with the least delay, and one that will maximize treatment en route. This is usually satisfied by a helicopter equipped to maintain intensive care in transit.

Surgical Debridement and Initial Hyperbaric Oxygen Treatment

Once transferred, a decision is made as to the necessity for surgery and, if required, whether it should be done before or after the first HBO treatment. We are convinced that adequate surgical debridement is essential and should be performed as soon as feasible. Often the patient can receive the initial HBO treatment during the time that an operating room is being prepared, typing and cross matching of blood performed, and an operating team assembled.

To monitor and medically manage the patient, a central venous line (Swan-Ganz) and an arterial line are strongly recommended before the first HBO exposure. We presently use monoplace chambers for HBO and use a pressure of 2.5 atm abs for 90 min for the initial treatment. This will give partial pressure of oxygen in the tissues above 250 mmHg, thereby favorably suppressing the bacteria and not exceeding the CNS oxygen toxicity threshold. The patient is decompressed and moved to the operating suite after the first HBO treatment if further surgery is required.

Conduct of surgery:

1. Nonviable tissue is removed.
2. Marginal tissues, if allowed to remain, must be evaluated at frequent intervals in the first 24 hours. We recommend 4-h intervals.
3. Meticulous hemostasis and removal of blood from the wound.

4. Remove foreign bodies from the wound.
5. Leave the wound wide open.
6. Wounds dressed with wet dressings with physiologic saline.

Note: Radical surgery as suggested by Freischlag et al. (83) is considered a step backward and should be relegated to the situation of mass casualties when hyperbaric chambers are unavailable.

Intense Combined Management

This is the most critical step in the management and is intense, requiring a dedicated and disciplined team to ensure that all parameters are observed. Medically, optimal fluid, blood, electrolyte, and antibiotic levels must be maintained. Potassium levels must be constantly monitored as hemolysis and tissue destruction may lead to hyperkalemia. A Swan-Ganz catheter should be placed into each toxic patient to properly assess fluid requirements.

Dressing changes with physiologic solutions (such as Ringer's irrigation) are performed at 4-h intervals or more frequently. The wounds must not be allowed to bathe in their own exudates because additional toxins will be absorbed and will delay recovery. Disinfectant solutions are not used as they will damage the compromised tissues at the wound margins (95-97).

Hemostasis must be maintained to prevent the release of catalase into the wound from red blood cells that would be utilized by the anaerobes to survive in a relative aerobic environment. Obviously nonviable tissue must be removed and may be debrided either locally on the ward or under general anesthesia in the operating room.

Hyperbaric oxygen treatments in a monoplace chamber are at 2.5 atm abs (36.75 psia) 90 min 3 times a day for 48 h, and reduced to 2.5 atm abs 90 min twice daily for 3 days followed by 2.0 atm abs (29.4 psia) 90 min twice daily. The recommended pressure in a multiplace chamber is 3 atm abs at the same intervals and length as above. HBO is continued until the infection is controlled, as evidenced by absence of toxicity, cessation of hemolysis, and a clean-appearing wound. This will usually require an additional 3 or 4 days of therapy.

Reconstruction and Rehabilitation

Antibiotics and HBO are discontinued. Grafting may be required and HBO is occasionally used to improve survival of compromised flaps or grafts.

Fallacies

1. All clostridia infections are gas gangrenes.
2. HBO cures gas gangrene.
3. HBO kills the clostridia organisms.
4. After the first HBO treatment the patient improves markedly.
5. HBO should be started before surgery.

Discussion

Questions frequently directed to the authors are:

1. The most frequent: *"What steps are taken to ensure that all patients received the same degree of antibiotic and surgical care?"*

The patients in our series were personally supervised by the authors and we have not changed antibiotic selection since the 1960s; the surgical procedures have become less radical since adding HBO to the regimen of care.

2. *"What type of chamber is recommended for treating gas gangrene?"*

We note little difference between a monoplace and multiplace chamber. The most important aspect is the physical presence of the chamber within the hospital so as to avoid interruption of management during transfer for HBO. The present generation of chambers (monoplace and multiplace) that are available in an intensive care unit are equipped to handle continuous monitoring.

3. *"Should one wait until the patient is normothermic, nontoxic, and normotensive to treat with HBO?"*

In our experience none were so critically ill that HBO could not be given. Forty-eight percent (67 patients) of those received in transfer, in our experience, arrived at the chamber in the classic state of shock with systolic blood pressures at 80 mm or less and/or requiring vasoactive iv.'s to maintain a reasonable blood pressure; 27 (40%) deaths occurred in this group. The only other patients that died after HBO were 3 that had suffered cardiac arrest elsewhere and HBO was given in a salvage attempt.

4. *"Is there a high incidence of oxygen toxicity in this group of patients?"*

We have had 1 patient with CNS oxygen seizure in the last 135 (0.7%) patients treated for gas gangrene. The patient was found to be in a state of metabolic acidosis and was treated with appropriate buffers; with this correction, the patient was treated without further seizures.

The factors associated with poor survival, such as delays in diagnosis, shock, and serious intercurrent medical problems, are recognized as contributing to morbidity and mortality, and success is measured by the aggressiveness of the team in managing the algorithm of care. It is apparent that with the present third-party restrictions, regulations from the government, and institutional gatekeepers, further delays and possible denials to care are irresponsibly increasing morbidity and mortality.

Conclusions

In summary, the reviewed studies indicate that HBO when applied early as an adjunct to antibiotics and surgery is the present standard of care for gas gangrene.

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