

## As a Characteristic of Recent Cases of Gas-forming Infection

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As a characteristic of recent cases of gas-forming infection, the incidence of non-clostridial gas-forming infection, which occurs non-traumatically, is increasing. This is in contrast to clostridial gas-forming infection that results from infection with clostridium, i.e., anaerobic gram-positive bacilli from a contaminated wound due to trauma. Diabetes mellitus is widely considered to underly the occurrence of non-clostridial gas-forming infection. The incidence is anticipated to increase further with the future increase in the number of diabetes mellitus patients in Japan. Since gas-forming infection is not common, the prognosis may worsen markedly because of delay in making a correct diagnosis and administering appropriate treatment. This report describes the diagnosis and treatment of 6 patients with non-clostridial gas-forming infection, experienced in our center, with reference to the literature.

### Introduction

Gas-forming infection is generally known as an uncommon disease developing at a contaminated wound site following trauma and at wounds associated with a hemokinetic disorder. Even at present approximately 10~20 cases are reported annually, in Japan, showing an increasing trend<sup>1)</sup>. Among the gas-forming infection cases occurring in recent times, the numbers of non-clostridial and non-traumatic cases are increasing, whereas those of clostridial gas-forming infection were more frequently seen in the past. Even if both clostridial and non-clostridial cases are included in the same category of gas-forming infection, they are different in terms of clinical course, symptoms, and therapeutic methods. The prognosis of the non-clostridial type is extremely poor unless it is treated early.

We encountered 6 patients with non-clostridial gas-forming infection, which has tended to in-

crease in recent years. These patients are reported with discussion of the relevant literature.

### Subjects

The subjects were 6 patients examined in our center during the past 4-year period. They were men, and their ages ranged from 48 to 75 years old, with a mean of 58.5 years old. Infected lesions were located in the right crus of 2 patients, the left crus of 2 patients, the left lower extremity of one patient, and the genital region of one patient (Fournier's gangrene). Five of these 6 patients had diabetes mellitus as the underlying disease. In 3 patients the gas-forming infection had progressed from diabetic gangrene. The species detected included *Klebsiella*, *Bacteroides*, *Enterococcus*, *Enterobacter*, *Streptococcus*, and others. All patients were treated by incision and debridement, and hyperbaric oxygen therapy. One also underwent disarticulation of the hipjoint, and 2, amputation at the level of the femur. Two patients ultimately

**Table 1** Underlying disease, infected lesion, pyogenic bacteria, treatment, and outcome of patients

Case No.	Age	Sex	Underlying disease	Infected lesions	Detected bacteria	Treatment	Outcome
1	61	M	Hypertension	Genital region	<i>Bacteroides</i> <i>Enterococcus</i> <i>Streptococcus</i>	HBO (+), Cefpirome Benzylpenicillin	Died of sepsis
2	56	M	Diabetes mellitus	Right crus	<i>Enterococcus</i> <i>Streptococcus</i>	HBO (+), Cefpirome Femoral amputation	Survived
3	75	M	Diabetes mellitus	Right crus	<i>Bacteroides</i> <i>Klebsiella</i>	HBO (+), Cefpirome Femoral amputation	Survived
4	54	M	Diabetes mellitus	Left crus	<i>Bacteroides</i>	HBO (+), Cefpirome	Survived
5	58	M	Diabetes mellitus Hypertension	Left crus	<i>Enterococcus</i> <i>Enterobacter</i>	HBO (+), Cefepime	Survived
6	48	M	Diabetes mellitus Hypertension	Left lower extremity	<i>Bacteroides</i> <i>Streptococcus</i>	HBO (+), Cefepime Hip joint amputation	Died of sepsis

HBO: hyperbaric oxygen therapy

died (Table 1).

### Case 1

**Patient:** A 61-year-old man.

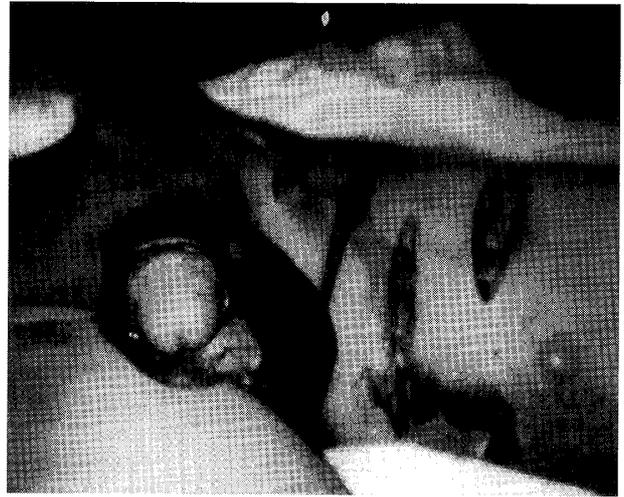
**Occupation:** Farmer.

**Past history:** Medicated for hypertension since age 57 years.

**Chief complaint:** Fever, right abdominal pain.

**Present illness:** From 9 days before transport to our center, he had had a fever (at least, 40°C) and right abdominal pain, and had been treated on an inpatient basis at a nearby hospital. From 3 days before transport to our center, he had swelling and erythema of the scrotum, which proceeded rapidly to invade the hypogastric and dorsal regions. The next day an offensive odor emanated from the scrotum. Local drainage was performed and the antibiotic was switched, but he went into shock. He was emergently transported to our center.

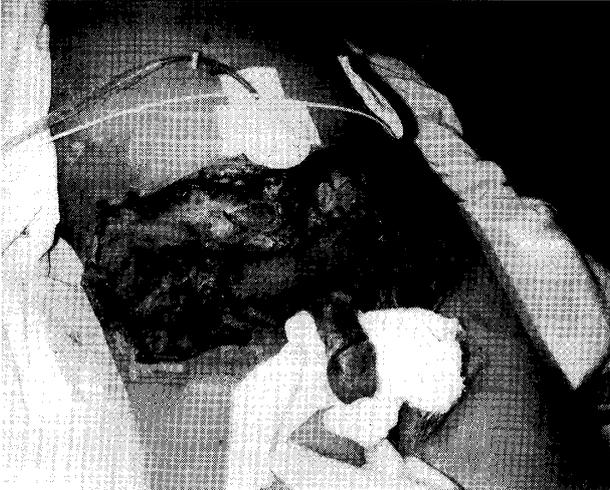
**Condition on admission:** The lesions of the left crus and a part of the hypogastric region had been treated by debridement in the previous hospital, as shown in Fig. 1. Edema, swelling, and erythema were present in the right and left femurs, lateroabdominal region, and dorsal region, and dermal necroses were also present in parts of these regions. His consciousness level could not be ascertained, because he was sedated. The



**Fig. 1** The lesions of the left crus and a part of the hypogastric region had been treated by debridement in previous hospital.

catecholamines used were dopamine (15 µg/kg/min), dobutamine (15 µg/kg/min), norepinephrine (15 µg/kg/min), and epinephrine (15 µg/kg/min). The blood pressure levels were 90/50 mmHg. Heart rate was 130 beats per minute, and temperature 38.3°C.

**Results of tests on admission:** Hematological tests revealed leukocytosis, mild anemia, hypoproteinemia, and metabolic acidosis. Elevated hepatic enzymes, creatine phosphokinase (CPK), blood urea nitrogen (BUN), creatinine (Cr), and C-reactive protein (CRP) were also noted. *Candida tropicalis* and *Enterobacter cloacae* were cultured



**Fig. 2** Wide-ranging debridement was added to the treatment.

from blood. Gram-positive cocci, gram-positive bacilli, and gram-negative bacilli were detected by gram staining of the pus from an open wound, which was performed on the day of blood culture (Table 2). On another day, large amount of cefpirome sensitive *Bacteroides fragilis* and cefpirome sensitive *Enterococcus avium/faecium* were isolated from the pus and identified.

**Clinical course:** From these findings, gas-forming infection was suspected in this patient, and non-clostridial Fournier's gangrene<sup>1)–3)</sup> was also suspected from the course observed in the previous hospital. When the patient was brought to our center, he was already in shock due to sepsis, respiratory insufficiency, renal insufficiency, and disseminated intravascular coagulation (DIC) syndrome. Wide-ranging debridement was added to the treatment because the gas was present to the crus as shown in Fig. 2. Continuous hemodiafiltration was promptly initiated for management of renal insufficiency, and hyperbaric oxygen therapy (2 atmospheres, 60 minutes) was performed for the shock and gas gangrene. The infection was treated with antibiotics, benzylpenicillin potassium and cefpirome sulfate, administration of which was combined with the use of

human immunoglobulin. Enormous numbers of segmental mycotic fila were observed to have survived in the tissue treated by wide-ranging debridement, and they were found to consist mainly of gram-negative cocci. The testis and epididymides were also affected by circulatory disorders, but there was no spread of inflammation to these organs.

From these findings and observations the patient's infection was diagnosed as non-clostridial Fournier's gangrene. Hyperbaric oxygen therapy is generally believed to be ineffective for non-clostridial gas-forming infection<sup>4)</sup>, but the therapy was continued for the purpose of improving the shock and adjunctively treating sepsis. We were apprehensive regarding fungemia given the pathological findings, and started to use an antifungal agent, fluconazole. Blood culture on the same day yielded *Candida tropicalis*, which had already been detected. Further debridement was impossible. The cultures performed on successive days revealed superinfection, and the patient ultimately died without relief of the infection. Respiratory insufficiency due to pneumonia on hospital day 18 (the 27th morbid day) was the immediate cause of death.

## Case 2

**Patient:** A 56-year-old man.

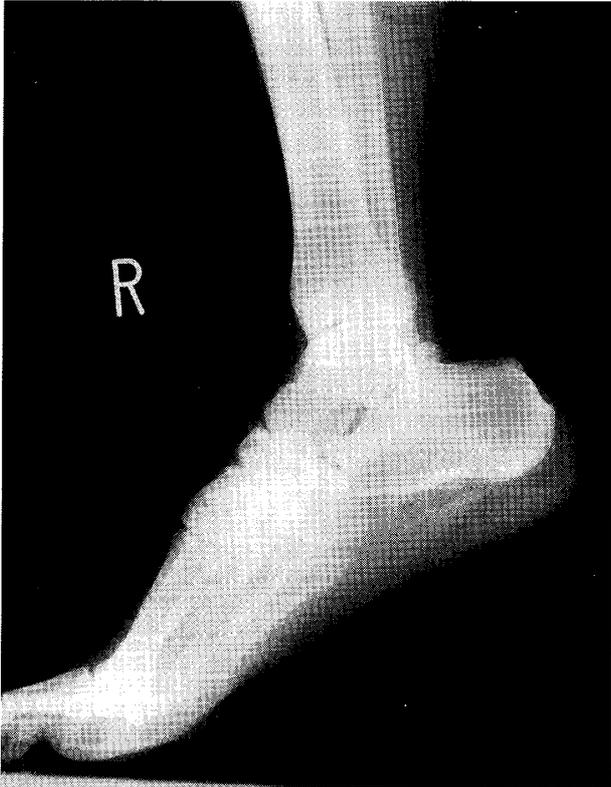
**Occupation:** Office worker.

**Past history:** Diabetes mellitus was well controlled with medication.

**Chief complaint:** Non-traumatic ulcers and pain of the right foot.

**Present illness:** The patient visited our center with chief complaints of non-traumatic ulcers and pain of the right foot. His consciousness was clear at the initial visit to our center. The underlying disease was diabetes mellitus under treatment. It was well controlled.

**Condition on admission:** Edema, swelling and erythema were present in the right crus, and der-



**Fig. 3** A roentgenogram of the right crus showed an image of grade 2 gas.

mal necroses were also present in parts of the involved areas.

**Results of tests on admission:** Hematological tests revealed leukocytosis, mild anemia, and elevated CPK and CRP. A roentgenogram of the right crus showed an image of grade 2 gas (Fig. 3).

**Clinical course:** The right crus was treated by incision and debridement to remove the necrotizing tissue immediately after admission. On this occasion, gas with a characteristic offensive odor and a serous exudate resembling bouillon were present. Cefpirome sensitive *Enterococcus avium/faecium* were detected from necrotizing tissue. The gas gangrene was treated by hyperbaric oxygen therapy (2 atmospheres, 60 minutes). The infection was treated with antibiotics, benzylpenicillin potassium and cefpirome sulfate, but the next day, the necrosis proceeded to invade the popliteal fossa. On hospital day 3, the fascial

inflammation spread to the center of the femur, but open amputation was performed at the center of the right femur taking into consideration that pylon application that would be employed later. The wound was treated by lavage twice a day and hyperbaric oxygen therapy (2 atmospheres, 60 minutes). On the 9th morbid day, the patient underwent stump formation for pylon application, and was discharged from our center.

### Case 3

**Patient:** A 75-year-old man.

**Occupation:** None.

**Past history:** Untreated diabetes mellitus.

**Chief complaint:** Non-traumatic pain of the right foot.

**Present illness:** The patient visited our center with a chief complaint of non-traumatic pain of the right foot. His consciousness was clear at the initial visit. The underlying disease was untreated diabetes mellitus.

**Condition on admission:** Edema, swelling and erythema were present in the right crus. Dermal necroses were present in some areas. The portion distal to the ankle was completely necrotic.

**Results of tests on admission:** Hematological tests revealed leukocytosis, mild anemia, hypoproteinemia, and elevated hepatic enzymes, BUN, Cr and CRP. The glycohemoglobin level was 12.8. A roentgenogram of the right crus showed an image of grade 3 gas.

**Clinical course:** The right crus was treated by incision and debridement to remove the necrotizing tissue immediately after admission. On this occasion, gas with a characteristic offensive odor and a serous exudate resembling bouillon were present. Cefpirome sensitive small amount of *Bacteroides fragilis* was detected from necrotizing tissue. On the same day, closed amputation was performed at the center of the right femur, followed by hyperbaric oxygen therapy (2 atmospheres, 60 minutes) for 5 days. Cefpirome sulfate was used

as the antibiotic. On the 21st morbid day, the patient underwent pylon application and was discharged from the hospital.

#### Case 4

**Patient:** A 54-year-old man.

**Occupation:** Teacher.

**Past history:** Diabetes mellitus was well controlled with medication.

**Chief complaint:** Non-traumatic pain of the left foot.

**Present illness:** The patient visited our center with chief complaints of non-traumatic pain of the left foot. The underlying disease was diabetes mellitus under treatment. It was well controlled.

**Condition on admission:** Swelling and erythema were present in the left crus.

**Results of tests on admission:** Hematological tests revealed mild leukocytosis, and elevated CPK and CRP. A roentgenogram of the left crus showed an image of grade 2 gas.

**Clinical course:** The left crus was treated by incision and debridement to remove the necrotizing tissue immediately after admission. On this occasion, gas with a characteristic offensive odor and a serous exudate resembling bouillon were present. Cefpirome sensitive small amount of *Bacteroides fragilis* was detected from necrotizing tissue. The gas gangrene was treated by hyperbaric oxygen therapy (2 atmospheres, 60 minutes). The infection was treated with antibiotics, benzylpenicillin potassium and cefpirome sulfate. The wound was treated by lavage twice a day and hyperbaric oxygen therapy (2 atmospheres, 60 minutes). On the 10th morbid day, the patient was discharged from our center.

#### Case 5

**Patient:** A 58-year-old man.

**Occupation:** Office worker.

**Past history:** Diabetes mellitus, hypertension with medication.

**Chief complaint:** Non-traumatic pain of the

left foot.

**Present illness:** The patient visited our center with a chief complaint of non-traumatic pain of the left foot. The underlying disease was uncontrolled diabetes mellitus and controlled hypertension.

**Condition on admission:** Edema, swelling and erythema were present in the right crus. Dermal necroses were present in some areas.

**Results of tests on admission:** Hematological tests revealed leukocytosis, hypoproteinemia, and elevated hepatic enzymes, and CRP. The glycohemoglobin level was 9.8. A roentgenogram of the left crus showed an image of grade 1 gas.

**Clinical course:** The left crus was treated by incision and debridement to remove the necrotizing tissue immediately after admission. On this occasion, gas with a characteristic offensive odor and a serous exudate resembling bouillon were present. Cefepime sensitive large amount of *Enterobacter cloacae* was detected from necrotizing tissue. On the same day, followed by hyperbaric oxygen therapy (2 atmospheres, 60 minutes) for 7 days. Cefepime sulfate was used as the antibiotic.

#### Case 6

**Patient:** A 48-year-old man.

**Occupation:** None.

**Past history:** Diabetes mellitus, hypertension.

**Chief complaint:** Edema and swelling of left lower extremity.

**Present illness:** The patient visited our center with a chief complaint of non-traumatic edema and swelling of left lower extremity. The underlying disease was uncontrolled diabetes mellitus and uncontrolled hypertension.

**Condition on admission:** Edema, swelling and erythema were present in the left lower extremity. Dermal necroses were present in some areas.

**Results of tests on admission:** Hematological tests revealed leukocytosis, hypoproteinemia, and

**Table 2** Clinical entities of gangrenous and crepitant cellulitis<sup>7)</sup>

Clostridial cellulitis*	Synonyms: Clostridial crepitant cellulitis, anaerobic cellulitis
Non-clostridial crepitant cellulitis*	Synonyms: Non-clostridial anaerobic cellulitis, anaerobic cellulitis, aerobic aerogenic infections, gas abscess
Necrotizing fasciitis*	Synonyms: Hemolytic streptococcal gangrene, streptococcal necrotizing fasciitis, gangrenous or necrotizing erysipelas, perineal phlegmon, Fournier's gangrene/syndrome
Progressive bacterial synergistic gangrene	Synonyms: Bacterial synergistic gangrene, Meleney's gangrene, postoperative progressive gangrene
Clostridial myonecrosis*^	Synonym: Gas gangrene
Non-clostridial myositis*^	Synonyms: (Anaerobic) streptococcal myositis, non-clostridial gas gangrene
Synergistic necrotizing cellulitis*^	Synonyms: Non-clostridial gas gangrene, synergistic non-clostridial anaerobic myonecrosis, perineal phlegmon, Fournier's gangrene/syndrome, necrotizing cutaneous myositis, gram-negative anaerobic cutaneous gangrene
Phycomycotic gangrenous cellulitis^	Synonym: Necrotizing cutaneous phycomycosis
Infected vascular gangrene^	
Miscellaneous types of gangrenous cellulitis in the compromised host*	

\*Tissue gas accumulation may be detected in these entities.

^Muscle involvement is prominent in these entities.

mild metabolic acidosis. Elevated hepatic enzymes, CPK and CRP were also noted. A roentgenogram of the left lower extremity showed an image of grade 2 gas.

**Clinical course:** The left lower extremity was treated by incision and debridement to remove the necrotizing tissue immediately after admission. On this occasion, gas with a characteristic offensive odor and a serous exudate resembling bouillon were present. The gas gangrene was treated by hyperbaric oxygen therapy (2 atmospheres, 60 minutes). The infection was treated with antibiotics, benzylpenicillin potassium and cefepime sulfate, but the next day, the necrosis proceeded to invade the upper lower extremity. On hospital day 2, the fascial inflammation spread to the upper of the femur. On the same day, closed amputation was performed at the hip joint. *Candida tropicalis* and *Enterobacter cloacae* were cultured from blood. Cefepime sensitive large amount of *Bacteroides fragilis* were detected of the amputated lower extremity. Respiratory insuffi-

ciency due to pneumonia on hospital day 42 was the immediate cause of death.

### Discussion

According to Brightmore et al<sup>5)</sup>, gas gangrene means gas-forming infection in a broad sense in the essential classification of gas gangrene. In a narrow sense, it means gas-forming infection with *Clostridium*, which is an anaerobic gram-positive coccus. Feingold<sup>6)</sup> classified gas-forming infection as shown in Table 3. At present, however, the incidence of gas-forming infection with *Clostridium* is decreasing while the incidence of non-clostridial gas-forming infection is increasing. Thus, there is a tendency for gas-forming infection to be classified into clostridial and non-clostridial gas gangrene types. However, there is a slight difference in the ways gas-forming infections are thought of between western countries and Japan. Gas-forming infection cases in Japan have been reported as minimal gas gangrene, but accurately speaking, gas gangrene shows infectious invasion to the muscle parenchyma. Ne-

**Table 3** Differentiation of gas gangrene

	Clostridial gas gangrene	Non-clostridial gas gangrene
Underlying disease	trauma	diabetes mellitus
Progression rate	rapid	gradual
Pain/Swelling	mild	severe
Redness	scarcely ever	mild
Transudate	serous fluid	pus, putrefaction
Tissue	myositis, myonecrosis	fasciitis, cellulitis, dermal gangrene
HBO	effective	effective

HBO: hyperbaric oxygen therapy

crotizing fasciitis is not gas gangrene. Thus, there would appear to be no problem even though gas-forming infection is either myonecrosis or necrotizing fasciitis. However, when the term, "gas gangrene" is used, it should be clearly distinguished from necrotizing fasciitis.

As shown in Table 3, gas gangrene is classified into clostridial (CGG) and non-clostridial (NCGG) according to the pyogenic bacteria. Most cases of gas gangrene have conventionally been CGG occurring after trauma, e.g., sustained in battle and traffic accidents. In recent years, the number of non-traumatic NCGG cases has been increasing<sup>7)</sup>. Approximately 70% of 70 NCGG patients reported for the 10 year period from 1987 through the end of 1996 in Japan had diabetes mellitus as an underlying disease. Five of our 6 patients also had diabetes mellitus. These observations show that the incidence of NCGG will increase further in the future along with an increase in the number of diabetes mellitus patients.

There are a variety of pyogenic bacteria that can cause NCGG, and the frequency of mixed infection with *Streptococci*, *Bacteroides*, *Peptostreptococci*, and *Enterococci* is particularly high<sup>8)</sup>. With regard to progression of the morbid condition, NCGG has a latent period of several days, as compared to that for CGG<sup>9)</sup>, and is believed to proceed slowly. However, in the presence of a mixed infection with *Streptococci*, which is favorable to growth of anaerobic bacteria<sup>10)</sup> the morbid condi-

tion of NCGG is believed to progress rapidly. NCGG is generally non-traumatic. The prognosis is also very poor, because the morbid condition has already been ongoing for some time at the manifestation of subjective symptoms.

Early differentiation and selection of the most appropriate therapeutic method are necessary for CGG and NCGG, because the therapy for CGG is slightly different from that for NCGG. In neither CGG nor NCGG, is there a significant difference in therapeutic method except the selection of antibiotics. It is therefore important to differentiate these disorders from the patient's clinical course before differentiation by bacterial culture and to initiate aggressive, early treatment. When gas gangrene is discussed according to sites, gas gangrene of the trunk is believed to have a high mortality rate, as compared to the mortality associated with gas gangrene of extremities, and to be generally serious.

Our personal case 1 had no problematic underlying disease but suffered from NCGG, which shows slow progression of morbid condition. Mixed infection with *Streptococcus* occurred 3 days before the patient was transferred to our hospital. The patient's condition was Fournier's gangrene of genital organs, the morbid condition of which proceeded at an appreciable rate. Failure in the lifesaving treatment for the patient was mostly due to a delay of approximately 9 days of making a diagnosis. The initial treatment

was delayed in our personal cases 1 and 6, and sepsis occurred, leading to the fatal courses. Our personal cases 2 through 5 received wound treatment, administration of antibiotics, and hyperbaric oxygen therapy immediately after the occurrence, and returned to their daily routine. Early diagnosis and early treatment are important in the control of severe infections showing a particularly short course.

The therapeutic method that we are proceeding involves wound treatment, administration of antibiotics, and hyperbaric oxygen therapy. For the wound treatment, it is important to remove the necrotic tissue first and to lavage the wound by appropriate incision and debridement. The treatment should be performed early on infections of the closed cavity. With regard to antibiotic administration, the absence of multiple drug resistance bacteria is indicated from the results of sensitivity test of isolates as well, which is performed in the early stage after the occurrence. Accordingly, the treatment should be initiated with antibiotics involving results of the sensitivity test.

In general, hyperbaric oxygen therapy for NCGG is varied with institutions, and there are also many who consider hyperbaric oxygen therapy ineffective<sup>4)11)</sup>. However, we hope that the hyperbaric oxygen treatment will exert effects to increase the leukocytic phagocytosis on the basis of the increased oxygen supplied to tissue cells and to facilitate wound healing<sup>7)10)</sup> as an effect on infections rather than that on anaerobic bacteria. The hyperbaric oxygen treatment should be performed as much as possible for other purposes as well, i.e., improvement of shock and adjuvant treatment of sepsis. A report by Myers et al<sup>8)12)</sup> has also shown that hyperbaric oxygen therapy is effective for severe infections as an adjuvant treatment.

Finally we should examine complaints of pedal

symptoms in diabetic patients on taking into consideration gas-forming infection as well, and endeavor to perform early treatment.

### Conclusions

1. Six patients with non-clostridial gas-forming infection were reported.
2. The incidence of non-clostridial gas-forming infection will be increasing along with the increase in diabetic patients.
3. Intensive treatment consisting mainly of wound debridement, antibiotic administration, and hyperbaric oxygen therapy must be initiated early for gas-forming infection. Non-traumatic gas-forming infection, in particular, has an extremely poor prognosis because it is likely to be diagnosed late.
4. The most important aspect of gas gangrene treatment is to increase the physician's recognition of this disease.

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### 最近のガス産生性感染症の動向

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最近のガス産生性感染症について、その考え方、特徴、治療について検討した。本邦においてのガス産生性感染症報告例ではガス産生性感染症をガス壊疽とし報告している向きが多く、壊死性筋膜炎とガス壊疽の区別がはっきりしていない。正確にはガス壊疽とはその感染が筋実質まで及ぶものであり、壊死性筋膜炎の状態ではガス壊疽ではない。よってガス産生性感染症としては、myonecrosis, necrotizing fasciitis のどちらかの状態であっても問題ないと考えられるが、gas gangrene を用いる場合は壊死性筋膜炎と明確に区別されるべきであると考えられる。

一般的にガス産生性感染症は外傷による汚染創、血流障害を有する創に発症する稀な疾患として知られている。しかし現在でも年間数十例程度の報告があり、年々増加を示している。最近のガス産生性感染症の特徴は、外傷による感染創からの嫌気性グラム陽性桿菌であるクロストリジウム属が感染し発症するクロストリジウム性ガス産生性感染症に変わって、非外傷性に発症する非クロストリジウム性ガス産生性感染症が顕著に増加している。非クロストリジウム性ガス産生性感染症はその背景に生活習慣病、特に糖尿病が強く関与しており、今後日本における糖尿病患者の増加に伴いさらに増えるものと考えられる。

また非外傷性ガス産生性感染症は、一般的な疾患でないために初診医の正しい診断および治療の遅れから著しく予後を悪くする場合があります。早期の診断加療が重要である。初療の遅れから、当センターにおいてわれわれが経験した重症度の高い非クロストリジウム性ガス産生性感染症例の検討から、早期の創処置、抗生物質投与、高気圧酸素療法を3本柱にした集中的治療が重要であると考えられる。