

# Features and treatment of gas-forming synergistic necrotizing cellulitis: a nine-year retrospective study

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## ABSTRACT

**BACKGROUND:** As many doctors know little about gas-forming synergistic necrotizing cellulitis, we retrospectively explored it in our study.

**METHODS:** Totally, 30 patients diagnosed with gas-forming synergistic necrotizing cellulitis between November 2006 and September 2015 were included. They were divided into two groups: open drainage group (19 patients) and aggressive debridement group (11 patients). Retrospectively analyzed data comprised demographic characteristics, APACHE II scores, pathogen culture results, bleeding amount during the operation, white blood cell count, length of hospital stay and recovery.

**RESULTS:** The mortality rate was 26% in the open drainage group and 73% in the aggressive debridement group ( $p=0.023$ ). There was no statistical difference in the APACHE II score before treatment between the open drainage and aggressive debridement groups ( $16.6\pm 4.5$  vs  $18.1\pm 7.5$ ,  $p=0.511$ ). The APACHE II score was significantly higher after treatment in the aggressive debridement group ( $14.2\pm 5.8$  score vs  $20.1\pm 9.1$ ,  $p=0.038$ ). There were no statistical differences in the white blood count cell before and after treatment ( $13.49 \times 10^9 \pm 5.05 \times 10^9$  cells/L vs  $17.46 \times 10^9 \pm 6.94 \times 10^9$  cells/L,  $p=0.082$ ;  $10.37 \times 10^9 \pm 3.54 \times 10^9$  cells/L vs  $15.47 \times 10^9 \pm 7.51 \times 10^9$  cells/L,  $p=0.055$ ; respectively). The bleeding amount during the operation was significantly more in the aggressive debridement group ( $315 \pm 112$  ml vs  $105 \pm 45$  ml,  $p<0.001$ ).

**CONCLUSION:** For treating gas-forming synergistic necrotizing cellulitis, performing open drainage as early as possible is the most important procedure after admission.

**Keywords:** Gas-forming infections; gas gangrene; synergistic necrotizing cellulitis.

## INTRODUCTION

Necrotizing fasciitis is a serious soft tissue infectious disease and is characterized by fascial necrosis and sepsis.<sup>[1]</sup> Based on the causative bacteria, it can be divided into two types: type I necrotizing fasciitis is caused by various bacteria, including gram-positive *Streptococcus hemolyticus* and *Staphylococcus aureus* and type II necrotizing fasciitis is generally monomicrobial and is typically caused by beta hemolytic *Streptococcus*.<sup>[2]</sup> Type I necrotizing fasciitis often occurs in the lower limbs; patients with diabetes and peripheral vascular disease are at

a high risk of developing this disease. Sometimes, the neck region or the perineum is also involved. Necrotizing fasciitis involving the perineum can rapidly spread to the abdominal wall, gluteal muscles, scrotum, and penis. Gas-forming synergistic necrotizing cellulitis is a special category of type I necrotizing fasciitis and is characterized by muscle involvement. *Bacillus cereus* has been demonstrated to cause this disease.<sup>[3]</sup> In clinical settings, gas-forming synergistic necrotizing cellulitis is always considered as gas gangrene. Many doctors believe that no advantage results from the distinction in regard to patient care.<sup>[4]</sup> In our opinion, gas-forming synergistic necrotizing cellulitis

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and gas gangrene are two different diseases. Gas gangrene has a unique treatment: (1) Extended resection is necessary, such as amputation. The real range of *Clostridium* infection is wider than it could be observed, extended resection must be done to control infection.<sup>[5]</sup> (2) Regarding anti-infective therapeutics, penicillin combined with clindamycin is effective against *Clostridium*.<sup>[6]</sup> Clindamycin treatment is highly effective in gas gangrene because gas gangrene is caused by an exotoxin whose synthesis is inhibited by clindamycin.<sup>[7]</sup>

While treating gas-forming synergistic necrotizing cellulitis, many doctors tend to perform aggressive debridement in the early period. In their opinion, aggressive debridement needs to be started as early as possible for getting rid of the necrotic tissue and toxins to improve the chance of patient survival. However, after doing this, many patients die because of massive hemorrhaging. Therefore, we conducted this retrospective study to find a better treatment and explored the features of this disease.

## MATERIALS AND METHODS

### Ethics

This study was approved by our local medicotechnical committee (Wenzhou Medical Association, Wenzhou, China).

## Data Collection

A retrospective review was performed on the medical records of all patients who were admitted to our hospital between November 2006 and September 2015 and who met the study criteria. Inclusion criteria were (1) serious infection of the lower limbs or perineum (Fig. 1a, b), (2) infection involving muscle layers, and (3) subcutaneous emphysema (Fig. 1c, d). Exclusion criteria were (1) incomplete clinical information (2) patients giving up treatment and (3) gas gangrene. Clinical data included age, gender, location of infection, underlying disease, APACHE II score, pathogen culture results, bleeding amount during the operation, white blood cell count, length of hospital stay, and recovery.

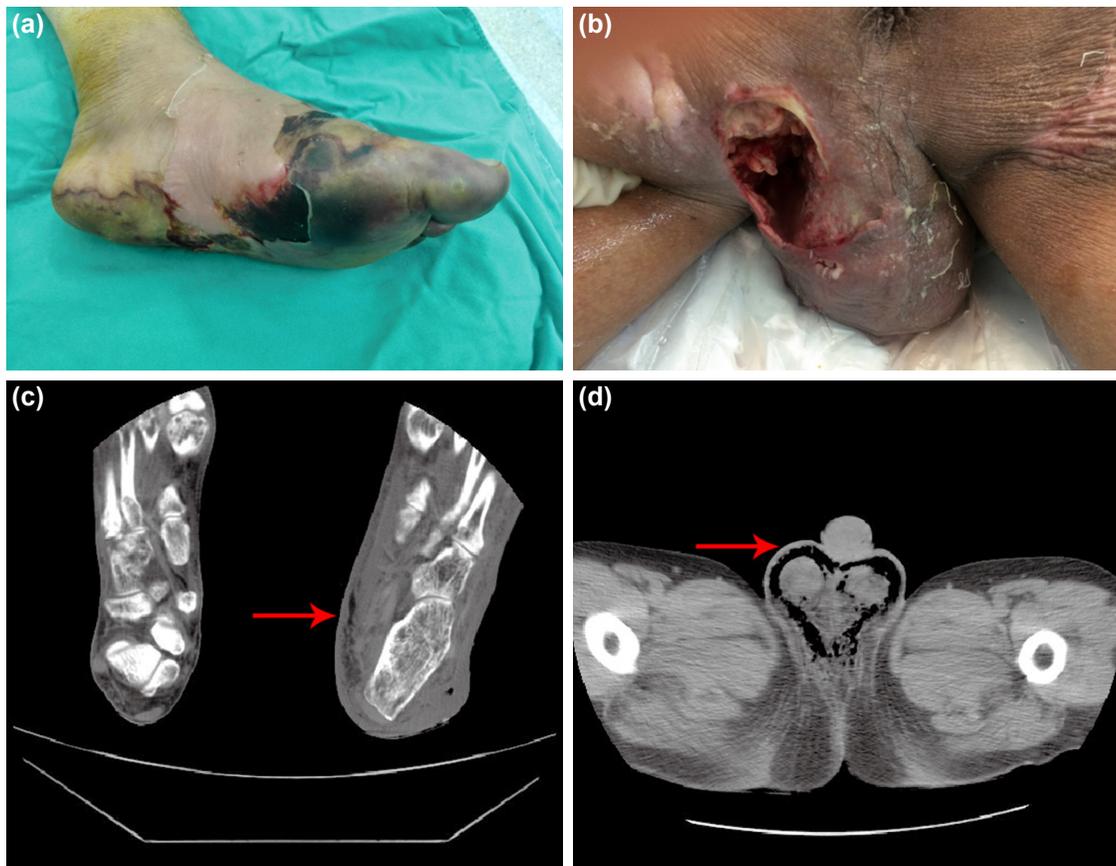
## Microbiological Methods

For pathogen cultures, blood agar and Sabouraud dextrose agar were utilized for all specimens. Physicians then selected the pathogens thought to be suitable. VITEK 2 Compact was used for identification. Minimum inhibitory concentrations were assessed during drug sensitivity tests.

## Treatment

### Early Stage Intervention

According to the medical records, 19 patients underwent



**Figure 1.** (a) The left foot was seriously infected, and the tissues were severely damaged. (b) The perineum was ruptured and exuded. (c) The left foot was overly swollen; radiography demonstrated soft tissue emphysema medially (arrow). (d) The scrotum had large amounts of gas in the radiograph (arrow).

**Table 1.** Patient characteristics and mortality rates in open drainage (n=19) and aggressive debridement (n=11) groups

Variable	Open drainage group			Aggressive debridement group			p
	n	%	Mean±SD	n	%	Mean±SD	
Sex, male	13	68		8	73		1.000
Age (years)			57.8±8.5			56.4±20.6	0.824
Liver disease	7	37		5	45		0.712
Diabetes mellitus	12	63		6	55		0.712
Location of infection, lower limbs	17	89		10	91		1.000
Mortality rate		26			73		0.023

SD: Standard deviation.

open drainage (open drainage group) and 11 underwent aggressive debridement (aggressive debridement group) as early as possible after admission. In the open drainage group, two ways were recommended for drainage: (1) incisions at the apparent position of crepitus. (2) removal part of necrotic tissues created open drainage. In the aggressive debridement group, all necrotic tissues were removed. Then, broad-spectrum antibiotics and support treatment were provided. Negative pressure wound therapy was not used for these wounds in the early duration.

### Later Stage Intervention

In the following days, dressings were changed and wounds were observed. A rapidly spreading infection was indicative of gas gangrene. Empiric treatment for gas gangrene was implemented, such as extended resection, anti-infective therapeutics (penicillin combined with clindamycin), and amputation. In case of gradual infection, patients were diagnosed with gas-forming synergistic necrotizing cellulitis. In the open drainage group, aggressive debridement was not performed until the vital signs became stable. The dressings were changed, necrotic tissues were removed, and bleeding amount was reduced by as much as possible. In the aggressive debridement group, the dressings were changed to promote granulation. Antibiotics were changed depending on culture results. Cultures from the 30 patients yielded 42 different species. The most prevalent organisms were *Staphylococcus* (n=6, 14.3%) (*Staphylococcus aureus*, *S. haemolyticus*, *S. epidermidis*, *S. hominis*), *Proteus* (n=6, 14.3%) (*Proteus vulgaris*, *P. mirabilis*), *Klebsiella pneumonia* (n=5, 11.9%), *Enterococcus* (n=5, 11.9%), *Stenotrophomonas maltophilia* (n=2, 4.8%), *Escherichia coli* (n=2, 4.8%), *Streptococcus* (n=2, 4.8%), *Citrobacter* (n=2, 4.8%), and *Corynebacterium* (n=2, 4.8%). *Acinetobacter baumannii*, *Raoultella planticola*, *Rhodococcus equi*, *Serratia marcescens*, *Pseudomonas mendocina*, *Morganella morganii*, *Enterobacter cloacae*, *Pseudomonas aeruginosa*, *Myroides*, and *Aeromonas caviae*. The wounds were finally repaired using skin grafting.

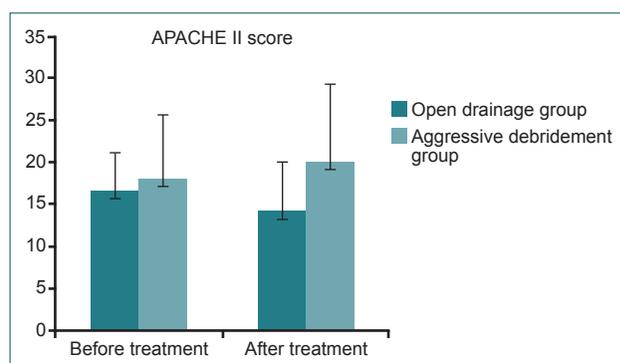
## RESULTS

### Patient Characteristics and Mortality Rates

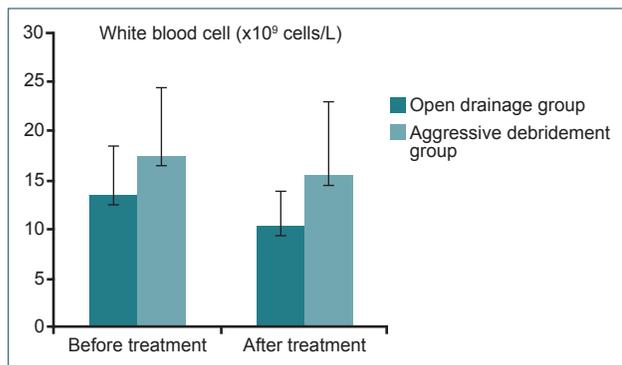
Thirty patients (21 males and 9 females) with a mean age of 57.3 years [standard deviation (SD), 13.8] were reviewed. Twenty-seven patients had infection that involved the lower limbs and three had infection that involved the perineum. Eighteen patients had diabetes mellitus and 12 had liver disease. The median APACHE II score after hospitalization was 17.2 (SD, 5.7). The median length of hospital stay was 29.2 days (SD, 23.7). A total of 13 patients died (mortality rate of 43%). Among the 14 patients who were successfully treated for infection involving the lower limbs, one underwent amputation. There was no statistical difference in terms of age, gender, underlying diseases (diabetes mellitus or liver disease), and position between the open drainage and aggressive debridement groups. The mortality rate was 26% in the open drainage group and 73% in the aggressive debridement group (Table 1).

### Changes in the APACHE II Score and White Blood Cell Count After Treatment and Bleeding Amount During the Operation

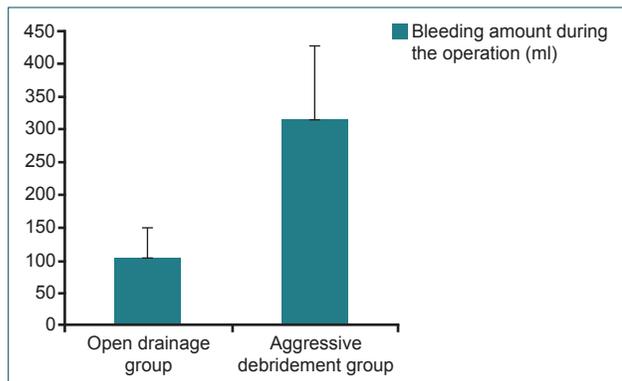
The APACHE II score was significantly higher after treatment



**Figure 2.** There was no statistical difference in the APACHE II score before treatment between the open drainage and aggressive debridement groups (16.6±4.5 vs 18.1±7.5, p=0.511). The APACHE II score was significantly higher after treatment in the aggressive debridement group (14.2±5.8 vs 20.1±9.1, p=0.038).



**Figure 3.** There was no statistical difference in the white blood cell count before and after treatment between the open drainage and aggressive debridement groups ( $13.49 \times 10^9$  cells/L  $\pm 5.05 \times 10^9$  cells/L vs  $17.46 \times 10^9$  cells/L  $\pm 6.94 \times 10^9$  cells/L,  $p=0.082$ ;  $10.37 \times 10^9$  cells/L  $\pm 3.54 \times 10^9$  cells/L vs  $15.47 \times 10^9$  cells/L  $\pm 7.51 \times 10^9$  cells/L,  $p=0.055$ ).



**Figure 4.** The bleeding amount during the operation was significantly less in the open drainage group ( $105 \pm 45$  ml vs  $315 \pm 112$  ml,  $p < 0.001$ ).

in the aggressive debridement group (Fig. 2). There was no statistical difference in the white blood cell count before and after treatment between the open drainage and aggressive debridement groups (Fig. 3). The bleeding amount during the operation was  $315 \pm 112$  ml in the aggressive debridement group, which was significantly higher than that in the open drainage group ( $105 \pm 45$  ml;  $p < 0.001$ ) (Fig. 4).

## DISCUSSION

Gas-forming synergistic necrotizing cellulitis is a very serious and rare disease. Surgery, antimicrobial therapy, and support treatment are essential early interventions. Surgery is thought to be the most important to improve the survival rate and should be conducted as early as possible.<sup>[8]</sup> Unfortunately, doctors do not know how to conduct the surgery. They think that aggressive debridement is the best way. After many years of treating patients with gas-forming synergistic necrotizing cellulitis, we have gained some experience. Gas-forming synergistic necrotizing cellulitis requires immediate surgery that needs to be started as early as possible to improve the chances of patient survival. Waiting for bacterial

culture growth, which takes several days, is not an option. During the operation, open drainage is the most important procedure; reducing the bleeding amount should also be considered. These patients always show unstable vital signs and poor coagulation function and cannot tolerate aggressive debridement. In our study, we found that the APACHE II score was significantly higher after treatment in the aggressive debridement group. The bleeding amount during the operation was significantly more in the aggressive debridement group. Based on the white blood cell count, we inferred that open drainage can also control inflammation and infection.

After the surgery, doctors must observe the wound and carry out the differential diagnosis of gas gangrene in the following days. Gas gangrene, as a gas-forming infection, is caused by *Clostridium*, which is a large gram-positive rod. Predisposing conditions for gas gangrene include local trauma or surgery; synergistic necrotizing cellulitis is often found in patients with diabetes mellitus and perirectal infection. The incubation period of gas gangrene is much shorter than that of synergistic necrotizing cellulitis, and the range of muscle infection is much larger in gas gangrene. In China, some doctors do not pay much attention to wounds in the early period; this results in death. For example, Wen treated five patients with gas-forming infections; one died because more attention was paid to the vital signs, ignoring the wounds. The others survived because the author observed the rapidly spreading wounds and treated them as gas gangrene.<sup>[9]</sup> Fu-Qiang treated seven patients; they all died because the author ignored the wounds and it was too late when they identified *Clostridium*.<sup>[10]</sup> After many years of treatment, we had accumulated experiences. On the first day, immediate open drainage and broad-spectrum antibiotics were administered. Subsequently, the wounds did not deteriorate, patients were diagnosed with gas-forming synergistic necrotizing cellulitis. We partly removed necrotic tissues when we changed the dressings. Until the vital signs stabilized, aggressive debridement was performed. Finally, the patients were cured. Negative pressure wound therapy is useful for treating wounds, such as diabetic foot.<sup>[11]</sup> However, there is little evidence that it can be used for gas-forming infections in the early period. In our opinion, it is inappropriate to control infection and inhibit aerogenic bacteria. If debridement is aggressively done in the later period, negative pressure wound therapy is a good option.<sup>[12]</sup>

Regarding the underlying diseases, the most frequent is diabetes mellitus. It was found in 60% of the patients in our study. Infectious wounds in diabetes are thought to be associated with neuropathy and angiopathy, and advanced glycation end products are initiating agents.<sup>[13,14]</sup> The reason why diabetes mellitus is a co-morbidity in patients with synergistic necrotizing cellulitis is unknown. In our opinion, advanced glycation end products may offer a good environment for the bacteria of synergistic necrotizing cellulitis, and diabetes patients have no resistance to the bacteria. Gender was proposed as another risk factor, with men having a higher chance

of being infected. This percentage was 70% in our study; however, some researchers showed there was no correlation.<sup>[15,16]</sup>

The major limitation of our study is that it was retrospective; a prospective study needs to be conducted. Another limitation is that the study did not assess many patients and that the patients were from one medical center; another further multi-institutional study to strengthen our findings is required. Despite these limitations, we found a new surgical procedure that is of great significance for treating gas-forming synergistic necrotizing cellulitis.

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Conflict of interest: None declared.

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## ORIJİNAL ÇALIŞMA - ÖZET

### Gaz oluşumuyla karakterize sinerjistik nekrotizan selülit özellikleri ve tedavisi: Dokuz yılı kapsayan geriye dönük çalışma

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**AMAÇ:** Birçok doktor gaz oluşumuyla karakterize sinerjistik nekrotizan selülit hakkında az bilgi sahiptir, çalışmamızda bu durumu geriye dönük araştırdık.

**GEREÇ VE YÖNTEM:** Kasım 2006 ile Eylül 2015 arasında gaz oluşumuyla karakterize sinerjistik nekrotizan selülit tanısı konmuş toplam 30 hasta çalışmaya alındı. On dokuz hastaya açık drenaj uygulandı, 11 hastaya agresif debridman yapıldı. Geriye dönük olarak demografiler, APACHE II skorları, patojenlerin kültür sonuçları, ameliyat sırasında kanama miktarı, beyaz küreler ve derlenme geriye dönük olarak incelendi.

**BULGULAR:** Ölüm oranları açık drenaj ve agresif debridman gruplarında sırasıyla %26 ve %73 idi (p=0.023). Tedavi öncesinde iki grup arasında APACHE II skorları açısından herhangi bir istatistiksel farklılık yoktu (16.6±4.5’e karşın 18.1±7.5, p=0.511). Tedavi sonrasında agresif tedavi grubunda APACHE II skoru anlamlı derecede daha yüksek idi (14.2±5.8’e karşın 20.1±9.1, p=0.038). Tedavi öncesi ve sonrası arasında beyaz küre sayısında istatistiksel farklılık yoktu (13.49±5.05×10<sup>9</sup> hücre/L’e karşın 17.46±6.94×10<sup>9</sup> hücre/L, p=0.082; 10.37±3.54×10<sup>9</sup> hücre /L ve 15.47±7.51×10<sup>9</sup> hücre /L, p=0.055). Ameliyat sırasında kanama agresif debridman grubunda anlamlı derecede daha fazla idi (315±112 ml’ye karşın 105±45 ml, p=0.000).

**TARTIŞMA:** Sinerjistik nekrotizan selülit tedavisi için hasta kabulden sonra olabildiğince en kısa sürede açık drenaj yapılacak en önemli girişimdir.

**Anahtar sözcükler:** Gaz oluşturan enfeksiyonlar; gazlı kangren; sinerjistik nekrotizan selülit.

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