Invited Review

Spontaneous Non-Traumatic *Clostridium perfringens* Sepsis

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SUMMARY: *Clostridium* species are gram-positive, spore-forming, anaerobic rods normally found in the soil and gastrointestinal tract of humans and animals. Spontaneous sepsis due to *C. perfringens* is not caused by injury, which sets it apart from the classical gas gangrene that typically follows trauma. Spontaneous *C. perfringens* sepsis often develops as a rapidly progressive intravascular hemolysis and metabolic acidosis, with high mortality rates of over 70% with standard intensive care. In such cases, alpha toxin secreted by *C. perfringens* is considered the main toxin responsible for intravascular hemolysis, disseminated intravascular coagulopathy, and multiple organ failure. Theta-toxin causes a cytokine cascade, which results in peripheral vasodilation similar to that seen in septic shock. For *C. perfringens* infections, antibiotics, such as high-dose penicillin, and surgical drainage as early as possible are the principal treatments of choice. However, considering the current mortality rate of sepsis, outcomes have not improved with the current standard treatment for *C. perfringens* infections. Monoclonal antibody against theta toxin in combination with gas gangrene antitoxin presents a promising therapeutic option.

1. Introduction

Clostridium perfringens is a gram-positive, anaerobic bacterium that grows in the gastrointestinal tract of humans and animals and is found in the soil (1). Spontaneous *C. perfringens* sepsis is not caused by injury, which sets it apart from the classical gas gangrene that typically follows trauma. Spontaneous sepsis due to *C. perfringens* often presents with rapidly progressive intravascular hemolysis and metabolic acidosis, with high mortality rates of above 70% with standard intensive care (2–11). In these cases, alpha-toxin secreted by *C. perfringens* is considered to be the main toxin responsible for intravascular hemolysis, disseminated intravascular coagulopathy (DIC) (12,13), and multiple organ failure. Although the number of reported cases with spontaneous *C. perfringens* sepsis is increasing (14–27), appropriate treatment strategies have not been established.

In this review, we aim to clarify the pathophysiology

and diagnosis of spontaneous *C. perfringens* sepsis and provide insights regarding treatment strategies, including antitoxin therapy.

2. Pathophysiology

At least 12 toxins are produced by *C. perfringens* types A, B, C, D, and E, with alpha, beta, epsilon, and iota as the major toxins (28). Recently, a French group was the first to report a case of a patient with septic shock due to peritonitis caused by *C. perfringens*; the case was complicated by massive hemolysis secondary to the secretion of alpha-toxin and theta-toxin by the bacterium (29). Alpha-toxin is a phospholipase C lecithinase that degrades phospholipids in the erythrocyte membrane, leading to subsequent accelerated destruction (14,30). Phospholipase C lecithinase may also cause platelet destruction, leading to thrombocytopenia. Conversely, theta-toxin is a cholesterol-dependent cytolysin that forms transmembrane pores; it also inhibits chemotaxis and the organized aggregation of neutrophilic granulocytes (29). Additionally, both alpha-toxin and theta-toxin affect the circulatory system. Specifically, alpha-toxin directly inhibits myocardial contractility whereas theta-toxin induces significant peripheral vasodilation (31). These toxic effects explain the characteristic fulminant shock observed in severe *C. perfringens* infection. The simultaneous presence of both toxins, which act

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Fig. 1. (Color Online) Clinical manifestations of spontaneous, non-traumatic *Clostridium perfringens* sepsis.

synergistically, is necessary for the development of serious *C. perfringens* infection (31,32). Thus, alpha-toxin and theta-toxin are considered the principal virulence factors of *C. perfringens* infection.

3. Diagnosis

Hemolysis is the first alarming sign of *C. perfringens* infection. The presence of a liver abscess with gas formation, accompanied by signs of hemolysis, such as increased levels of indirect bilirubin and lactate dehydrogenase, and anemia are typical manifestations; however, progression to gross hemolysis usually leads to death (Fig. 1) (33,34). Therefore, rapid diagnosis is essential and definitive diagnosis before the patient progresses to gross hemolysis is crucial. Considering the pathophysiology of *C. perfringens* infection, early detection of alpha-toxin and theta-toxin in the serum might be the key to diagnosis. Monoclonal antibodies against these toxins, which have already been used in research settings, might be utilized for the development of diagnostic assays. Clinicians should always suspect *C. perfringens* sepsis in the absence of overt signs of hemolysis in patients with liver abscesses accompanied by gas formation.

In addition to the analysis for the presence of toxins, the diagnosis of DIC is also important for deciding whether adjunctive therapy should be initiated. The diagnosis of DIC is based on the criteria established by the Japanese Association for Acute Medicine (35,36), with a total score ≥ 4 indicating DIC.

4. General treatment strategies and adjunctive therapies

For bacterial infection, antibiotics, such as high-dose penicillin, and surgical drainage as early as possible are the 2 main treatments of choice (30). However, considering the high mortality rate of sepsis (37), the currently utilized standard treatments for *C. perfringens* infection have not led to better outcomes. To further improve patient outcomes, focusing on specific treatments is a reasonable first step in establishing therapeutic strategies with acceptable clinical outcomes.

Recombinant human soluble thrombomodulin (rTM) has been shown to be effective for sepsis-induced DIC in a meta-analysis (38). We previously examined the effects of rTM on hemolysis, coagulation status, inflammation, and mortality in alpha-toxin-treated rats (39) and found that rTM improved coagulation response induced by alpha-toxin with a significant difference in FDP level and platelet count in the rTM-treated group compared with the alpha-toxin-only group (39). These results suggest rTM as a candidate for the treatment of *C. perfringens*-induced DIC because it serves as a negative feedback regulator of blood coagulation (40).

Recently, Kubo et al. reported 2 patients with liver abscesses caused by *C. perfringens* who were initiated on intensive plasma exchange and survived (41). The application of plasma exchange to remove excess toxins produced by *C. perfringens* is reasonable. In fact, patients with Yamakagashi snake bites survived with aggressive plasma exchange therapy (42). However, in real-world clinical settings, especially for patients in septic shock, dialysis may cause severe hypotension,

which may necessitate therapy suspension. Thus, alternative therapies should be considered in patients with septic shock due to *C. perfringens*.

5. Antitoxin therapy

The gas gangrene antitoxin, which was developed against the toxins produced by *C. perfringens* type A, *C. septicum*, and *C. oedematiens*, has been used as a treatment option for classical gas gangrene following trauma. However, this product is no longer available in the United States due to its poor efficacy and severe allergic reactions against it. The gas gangrene antitoxin can neutralize alpha-toxin secreted by *C. perfringens*. Therefore, we have introduced and strongly recommended the use of the gas gangrene antitoxin as the optimal therapy in *C. perfringens* sepsis based on its pathophysiological mechanism (34,43,44). In a study investigating the effects of gas gangrene antitoxin on hemolysis, coagulation status, inflammation, and mortality in alpha-toxin-treated rats, we demonstrated that the gas gangrene antitoxin could stop hemolysis via the neutralization of alpha-toxin (39).

In a clinical setting, Yoshida et al. was the first to report a patient with *C. perfringens* sepsis who was treated with gas gangrene antitoxin (45). However, the efficacy of the gas gangrene antitoxin remains unclear because it was administered after the patient developed cardiopulmonary arrest and the patient died 8 h after gas gangrene antitoxin administration.

The gas gangrene antitoxin is owned by the government under the name of Kokuyu vaccine (34), and stored in 9 institutions spread across Japan. Therefore, rapid administration of the gas gangrene antitoxin is not practical due to supply limitations. In future, the gas gangrene antitoxin stocks at major hospitals, such as university hospitals and national hospital organizations, should be considered to treat patients with spontaneous *C. perfringens* sepsis.

The clinical use of the monoclonal antibody against theta-toxin, developed and defined first by Yamakawa et al. (46), in combination with the gas gangrene antitoxin is a promising therapeutic approach for spontaneous *C. perfringens* sepsis.

6. Prevention

Considering the high mortality rate with the currently used standard therapy, prevention strategies may be more practical than the development of promising monoclonal antibodies. As the first step in prevention, vaccination is considered the principal component. Four doses of the diphtheria/tetanus/pertussis vaccine are administered during infancy, and a vaccine against diphtheria and tetanus is administered at the age of 11–12 years under the Preventive Vaccination Law enacted in 1968 in Japan; this led to the disappearance of the diphtheria infection from clinical practice (47,48). Currently, there are no licensed vaccines that are suitable for protecting against *C. perfringens* sepsis in humans (49). However, vaccines that are currently in development for use in animals can potentially be developed further for use in humans (49,50). Therefore, vaccination might be considered an effective strategy

for protection from serious *C. perfringens* sepsis in humans.

7. Future considerations

There is no nationwide registration for *C. perfringens* sepsis in Japan. Therefore, the exact number of patients with *C. perfringens* sepsis remains unknown. We recently launched a research group supported by the Research Program on Emerging and Re-emerging Infectious Disease of the Japan Agency for Medical Research and Development, with the aim of examining spontaneous *C. perfringens* sepsis in 2019. The creation of a nationwide registry for *C. perfringens* sepsis is the first step in the establishment of effective treatment strategies and further urgent work will be required.

8. Conclusion

In this review, we provided an overview of the pathophysiology and diagnosis of spontaneous *C. perfringens* sepsis, and provided currently utilized treatment strategies including the gas gangrene antitoxin, which can be administered as early as possible in combination with antibiotics to neutralize the toxins.

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Conflict of interest None to declare.

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