

Review Article

Article de revue

GROUP A *STREPTOCOCCUS* INVASIVE INFECTIONS: A REVIEW

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The incidence of group A *Streptococcus* (GAS) invasive infections has been increasing worldwide, and there is no obvious explanation for this phenomenon. In 1993, a working group on severe GAS infections was established to define accurately what constitutes an invasive infection. Three types of infection are particularly feared: necrotizing fasciitis, myositis and a newly defined entity, named streptococcal toxic shock syndrome (STSS) because of a certain analogy with its staphylococcal counterpart. GAS produces many toxins responsible for its clinical manifestations. Some of them, labelled streptococcal pyrogenic exotoxins, have been characterized as superantigens. These proteins play a key role in initiating the immune response to GAS and are mostly responsible for the precipitous course of invasive infections. Death rates are high in streptococcal invasive infections, ranging from about 20% for necrotizing fasciitis to almost 100% for myositis. Therapy consists mainly of high doses of antibiotic combinations, aggressive surgery, and intravenous administration of immunoglobulins for STSS.

L'incidence d'infections invasives à *streptocoque* du groupe A (SGA) est à la hausse partout dans le monde et il n'y a aucune explication évidente de ce phénomène. En 1993, un groupe de travail sur les infections invasives graves à SGA a été chargé de définir avec précision ce qui constitue une infection invasive. On craint en particulier trois types d'infection : la fasciite nécrosante, la myosite et une entité qui vient d'être définie, soit le syndrome de choc toxique streptococcique (SCTS), appelé ainsi à cause d'une certaine analogie avec son homologue staphylococcique. Le SGA produit de nombreuses toxines qui en causent les symptômes cliniques. Certaines de ces toxines, appelées exotoxines pyrogènes streptococciques, ont été qualifiées de superantigène. Ces protéines jouent un rôle clé dans le déclenchement de la réaction immunitaire au SGA. Elles ont la principale cause d'accélération des infections invasives. Les taux de mortalité sont élevés dans les cas d'infection invasive à streptocoque et varient d'environ 20 % dans le cas de la fasciite nécrosante jusqu'à presque 100 % dans celui de la myosite. Le traitement comporte surtout des doses élevées de combinaisons d'antibiotiques, une chirurgie agressive et l'administration par voie intraveineuse d'immunoglobulines contre le SCTS.

Over the last decade, a growing number of severe invasive group A *Streptococcus* (GAS) infections have been reported.¹⁻⁴ The exact definition of GAS invasive infections was established by a special task force in 1993 (Table I).⁵ Invasive infections comprise a large and diverse group of disease entities, including cel-

lulitis, necrotizing fasciitis and myositis, often referred as "flesh-eating disease" by the media. All these diseases can be complicated by a dreaded entity — the streptococcal toxic shock syndrome (STSS). The reasons for the sudden emergence of these invasive infections are still unknown.

Early recognition of these diseases

and a rapid initiation of the appropriate treatment are important steps in patient survival. Surgery plays a key role in the management of many of these infections and is an essential part of therapy. The reported death rate for invasive GAS infections is high (Table II^{3,6-14}).

In this review we focus on the gen-

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eral aspects of GAS invasive infection, as well as on certain entities, such as necrotizing fasciitis and myositis. We review all therapeutic avenues, old and new, relevant to the treatment of GAS infections.

HISTORICAL PERSPECTIVE

GAS was first described in 1874 by Billroth, who demonstrated its presence in wound infections and erysipelas. Pasteur identified GAS as the cause of puerperal sepsis in 1879. In 1884, Rosenbach gave it the name *Streptococcus pyogenes*. Lancefield made a major contribution in the field of epidemiology in 1933, when she classified β-hemolytic streptococci in different groups.

Throughout history, GAS has been responsible for major epidemics with catastrophic consequences.¹⁵ With the advent of better hygiene, penicillin and modern medicine, there was a striking drop in the incidence of severe GAS infections.^{15,16} Now, for unknown reasons, there has been a surge

of severe, life-threatening infections, notably in developed countries.

In Sweden, the number of cases of GAS bacteremia per 100 000 population jumped from 1.8 in 1987 to 2.4 in 1989.² In Arizona, a study conducted between January 1987 and March 1990 showed an annual age-adjusted incidence of GAS invasive infections of 4.3 per 100 000 population. But the infection rate was much higher among native Americans (46 per 100 000).¹⁷ In 1992, the annual incidences in Ontario of invasive GAS infections and STSS were 1.15 and 0.19 per 100 000 population respectively.¹ In 1994, a definite increase in the number of cases of necrotizing fasciitis was noted compared with previous years.

THE PATHOGEN AND PATHOPHYSIOLOGY

GAS is a gram-positive coccus that produces and has numerous constituents, somatic and extracellular, capable of an important role in the pathogenesis of the invasive infection.

First, certain proteins are produced and expressed at the surface of the bacterium, notably the M protein, which is a major virulence factor. This antigen has the ability to decrease phagocytosis by polymorphonuclear leukocytes and plays an important role in initiating the streptococcal diseases. There are about 80 different types of M protein. Not all group A streptococci carry the M protein, some are called non-typable and are considered to be less virulent. Another important surface antigen is called the serum opacity factor (SOF), so named because of its ability to opacify horse serum. For more precise typing and identification purposes, another protein called T protein has been identified by Griffith.¹⁸ Apart from its epidemiologic importance, this protein has no virulence potential.

Extracellular toxins are produced by GAS and represent essential mediators of the bacterial virulence. Among them are the streptococcal pyrogenic exotoxins (SPEs). Three different types of SPEs have been characterized and named A, B and C. These toxins have been shown, experimentally, to induce cytotoxicity and to provoke symptoms comparable to those seen in the staphylococcal toxic shock syndrome. SPE-A and the staphylococcal toxic shock syndrome toxin-1 (TSST-1) have a similar molecular structure.¹⁹

The pathophysiology of severe GAS infections is not fully understood, but SPEs are playing a key role as super-antigens (bacterial products, mainly from gram-positive bacteria that have the ability to massively stimulate non-specific T-cell proliferation).^{11,20,21} The T-cell proliferation, once activated, enhances the production of cytokines. Large production of tumour necrosis factor (TNF) and interleukins (1β and 6) mediate fever, shock, tissue injury and the spectacular inflammatory process seen in STSS. SPEs can trigger

Table I

Classification of Group A Streptococcal (GAS) Infections

Class	Description
I	Streptococcal toxic shock syndrome (as defined in Table II)
II	Other invasive infections in patients not meeting criteria for streptococcal toxic shock syndrome
A	Bacteremia with no identified focus
B	Focal infections with or without bacteremia. Includes meningitis, pneumonia, peritonitis, puerperal sepsis, osteomyelitis, septic arthritis, necrotizing fasciitis, surgical wound infections, erysipelas and cellulitis
III	Scarlet fever
IV	Noninvasive infections: defined by the isolation of GAS from a non-sterile site
A	Mucous membrane: pharyngitis, tonsillitis, otitis media, sinusitis, vaginitis
tB	Cutaneous: impetigo
V	Nonsuppurative sequelae
A	Acute rheumatic fever
B	Acute glomerulonephritis

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such a response because of their ability to cross-link the major histocompatibility complex (MHC) molecule on antigen-presenting cells, with the variable region of the T-cell receptor β chain (Fig. 1). Compared with conventional antigens, superantigens are unique in that they can activate a T cell without being previously processed by an antigen-presenting cell. Besides, specific interaction between conventional antigens and T cells is governed by the 5 variable regions of the T-cell receptor ($J\alpha$, $V\alpha$, $J\beta$, $D\beta$, $V\beta$), whereas the coupling of superantigens with T cells is primarily under the control of only the $V\beta$ region, with little contribution from the other regions of the T-cell receptor. Thus, a conventional antigen usually activates less than 0.01% of all T cells; in contrast, a superantigen can stimulate between 5%

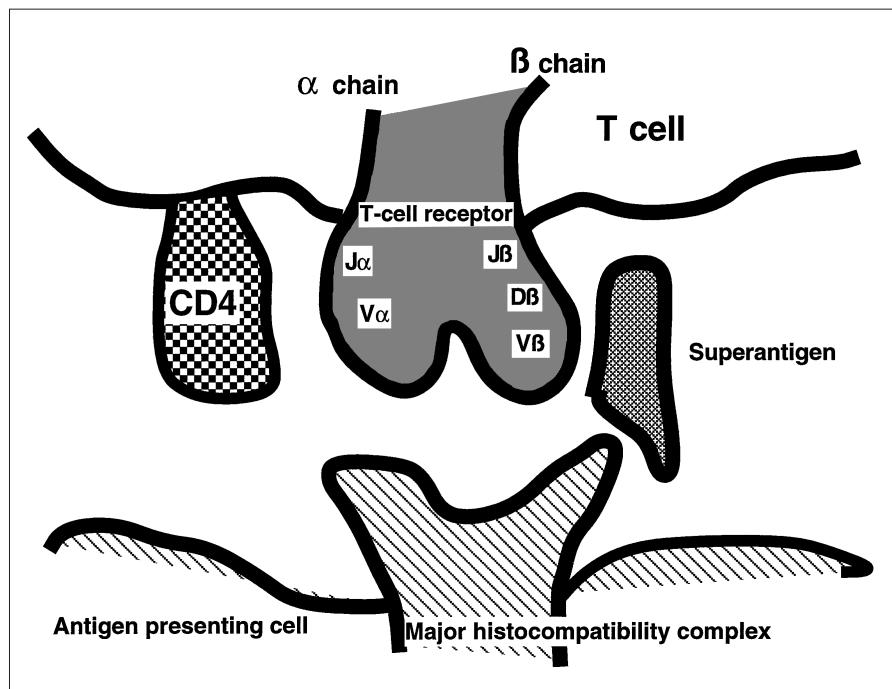


FIG. 1. A model of superantigen interaction with a T cell and major histocompatibility complex molecule. $J\alpha$, $J\beta$, $V\alpha$, $V\beta$ and $D\beta$ = five regions of the T-cell receptor.

Table II

Death Rate for GAS Invasive Infections in the Literature

Series	Disease	No. of patients	Death, no. (%)	Comments
Yoder, Mendez, Khatib, 1987 ⁶	M	11	11 (100)	Leg involved in 73% of cases
Barker, Leppard, Seal, 1987 ⁷	NF	16	5 (31)	—
Stevens et al, 1989 ³	STSS	19	6 (32)	74% of patients had surgery. No underlying disease in 65% of patients
Farley et al, 1990 ⁸	NF, STSS	15	4 (27)	Predisposing factor: 65% of cases with non-intact skin
Wheeler et al, 1991 ⁹	B	33	2 (6)	Pediatric cases. Bacteremia seemed less severe in children than adults.
Demers et al, 1991 ¹⁰	NF, M, B, STSS	42	22 (52)	Ontario study (1987–1991)
Stevens, 1992 ¹¹	B	573	214 (37)	11 case series (1937–1991), mostly associated with soft-tissue infection
Stevens, 1992 ¹¹	NF	78	21 (27)	Combination of 5 case series. Minor trauma very frequent
Chelsom et al, 1994 ¹²	NF	13	3 (23)	Aggressive surgery advised
Brogan et al, 1995 ¹³	NF	14	0	Pediatric cases, hyperbaric chamber used with subjective benefit
Forni et al, 1995 ¹⁴	STSS	6	3 (50)	Distinctive hemodynamic profile

NF = necrotizing fasciitis, M = myositis, B = bacteremia, STSS = streptococcal toxic shock syndrome

and 40% of all T cells.²⁰

CLINICAL SPECTRUM

Necrotizing fasciitis

Necrotizing fasciitis is a deep-seated skin infection that destroys all the anatomic structures, from superficial skin to muscle fascia.²² It is characterized by extensive and rapidly progressing gangrene of the skin and underlying structures. Necrotizing fasciitis is mostly caused by mixed aerobic and anaerobic floras, giving an average of 4.6 isolates per specimen.²³ In a study evaluating the microbiologic aspect of necrotizing fasciitis, GAS was recovered in only 8 of 83 patients.²³ In this review, we will focus solely on GAS necrotizing fasciitis.

The first physician to describe GAS necrotizing fasciitis was a German surgeon during the First World War, who reported a case of necrotizing erysipelas in 1918.²⁴ In 1924, Meleney²⁵ was the first to accurately characterize this entity in previously healthy young adults who suddenly became seriously ill and required emergency surgical intervention. In his series of 20 cases, the death rate was 20%, although he had no antibiotics to treat patients; only surgery and irrigation with Dakin solution were used. Moreover, he advocated an immediate and aggressive "bear scratch" surgical débridement. The standard clinical description of GAS necrotizing fasciitis is a rapidly progressing infection, starting at the site of minor or inapparent trauma. Bullae containing yellow or bloody fluid subsequently appear. Bacteremia is often present, and metastatic abscesses may develop. Fasciitis often follows a penetrating injury or surgery; 80% of the patients report a traumatic incident in the days preceding the onset of their infection. Thus, it is essential to seek a history of trauma of any kind when questioning

the patient.

Following the original report by Meleney, several others described the condition, reporting a death rate ranging from 10% to 50%.^{3,26,27} The higher death rate reported today is mainly the result of shock and multiorgan failure, which was not an issue in Meleney's time. The recent emergence of GAS strains with increased virulence factors is a possible explanation.

Necrotizing fasciitis has also been linked to primary varicella infection in previously healthy children.¹³ In this 14-patient series, hyperbaric oxygen therapy was used in 12 patients, 6 of whom had subjective benefit.

Necrotizing fasciitis management is based primarily on recognition of the disease. A high degree of suspicion is necessary; clinical hints such as a progressing cellulitis in an adequately treated patient or pain that is disproportionate to the degree of cellulitis are ominous signs. Differentiation between cellulitis and necrotizing fasciitis is not easy. However, as surgical management of the two diseases is quite different, patients must be carefully assessed and monitored. Some have suggested that rapid performance of frozen-section soft-tissue biopsy early in the evolution of a suspected necrotizing fasciitis, may be lifesaving.²⁸ The identification of certain histologic characteristics of necrotizing fasciitis would hasten surgical intervention and could have a significant impact on the death rate.²⁸

Myositis

In the medical literature, streptococcal myositis is rarely reported.^{6,11,29} This condition should not be confused with a disease known as pyomyositis, which is well described, quite frequent in subtropical or tropical areas and caused mostly by *Staphylococcus aureus* or occasionally GAS.

In North America, this condition has recently been linked to HIV-infected people.³⁰ This infection mainly affects large-muscle groups and is not associated with the fulminant and deadly outcome of standard GAS myositis.

So far there have been only about 30 reported cases of β-hemolytic streptococcal myositis, most of them caused by GAS. This disease, fortunately very rare, has a death rate varying between 80% and 100%. There is no sex predilection, the age distribution is wide and there are no specific predisposing factors.

Muscle infection seems to be a very difficult condition to achieve experimentally. In 1923 Halsted³¹ could not induce muscle injury by compromising the vascular supply and injecting *S. aureus* into dog muscles. Moreover, in streptococcal septicemia, muscle involvement is exceptional. Traumatic injury may be a triggering factor in certain types of myositis but has not been implicated in streptococcal myositis. Streptococci are known to produce a number of enzymes and toxins that may contribute to the pathogenesis. Notably, the production of hyaluronidase, which splits hyaluronic acid (a major substance in connective tissue), seems to play a major role in the disease propagation.

The clinical features of streptococcal myositis are not specific. They are characterized by spontaneous onset of pain occurring in the affected muscle, followed by erythema, exquisite tenderness, swelling, decreased motion and fever, all appearing rapidly. Compartment syndrome can be present and should heighten the likelihood of the disease. It is extremely difficult to distinguish between necrotizing fasciitis and myositis. Muscle necrosis is the key differentiating these conditions, and this pathological difference may be arbitrary in a clinical setting. Nevertheless, there is a major differ-

ence between these diseases with regard to the final outcome, which is much worse in myositis (85% v. 16% death rate).⁶ Moreover fasciitis responds much better to therapy and often does not have the rapidly invasive course of myositis. Myositis therapy consists of high-dose intravenously administered antibiotics and early, extensive surgical débridement. Surgery plays a central role in the management of myositis, because antibiotics alone are ineffective in such cases.^{3,6,27-29} Differentiating GAS myositis from *Clostridium* species (*Clostridium perfringens*, *Clostridium septicum*) gas gangrene is also difficult, although the presence of crepitus favours the latter.

STSS

This represents the most dreaded infection due to GAS. In the late 1980s, cases started to be described in the United States,^{2,3} Scandinavia⁴ and Canada.¹ In Canada, cases have been reported in Prince Edward Island,³² Quebec,³³ Ontario¹ and British Columbia.⁸ The clinical manifestations of this infection are similar to those of the staphylococcal toxic shock syndrome.³⁴ The exact definition of the syndrome has been established by using both clinical and laboratory criteria (Table III). Adults between the ages of 20 and 50 years seem to be the most affected, and these patients tend to have no previous underlying diseases. This is in sharp contrast to previous reports of GAS bacteremia, in which patients were mostly at the extremes of life (newborns and elderly) and had underlying medical conditions, such as cancer or severe burns or were immunosuppressed.¹¹ The acquisition of GAS in such cases is mainly through the mucous membranes or skin, but in up to 50% of the patients, no specific portal of entry can be pinpointed. Symptomatic pharyngitis or vaginal in-

fection in women was rarely noticed in the STSS prodrome.

A nonspecific influenza-like syndrome precedes the onset of STSS by several days in many patients. Between 60% and 80% of patients will have evidence of soft-tissue involvement at one point during the course of the infection. Complications occur quite frequently; adult respiratory distress syndrome will develop in 55% of patients and renal impairment in 80%.¹¹ The death rate varies between 30% and 80%.^{1-3,11} An interesting observation made by Forni and associates¹⁴ was a distinct early hemodynamic profile in STSS patients that was consistent with toxic cardiomyopathy (relatively low cardiac output, low-to-normal sys-

temic resistance and a significant reduction in ventricular performance). This difference, similar to the standard hemodynamic profile found in gram-negative septic shock, may be explained by SPEs having myocardial depressant properties.¹⁴

Serologic studies of strains involved in STSS have shown that M-protein types 1 and 3 are most commonly isolated. Types 12 and 28 have also been reported in cases of toxic shock. Moreover, SPE A or B, or both, are found in the majority of patients with severe GAS infections.^{1-4,11,20}

TREATMENT

Severe GAS infections tend to be

Table III

Case Definition for the STSS

Criterion	Description
I	Isolation of group A streptococci (<i>Streptococcus pyogenes</i>)
A	From a normally sterile site (blood, cerebral spinal fluid, tissue biopsy, surgical wound, pleural or peritoneal fluid)
B	From a nonsterile site (throat, sputum, vagina, superficial skin)
II	Clinical signs of severity
A	Hypotension: systolic blood pressure \leq 90 mm Hg in adults or $<$ 5th percentile for age in children/and
B	2 of the following signs
	1. Renal impairment: creatinine \geq 177 $\mu\text{mol/L}$ for adults or \geq twice the upper limit of normal for age. In patients with preexisting renal disease, a twofold elevation over the baseline level
	2. Coagulopathy: platelets \leq $100 \times 10^9/\text{L}$ or disseminated intravascular coagulation, defined by prolonged clotting time, low fibrinogen level and the presence of fibrin degradation products
	3. Liver involvement: alanine aminotransferase, aspartate aminotransferase or total bilirubin levels \geq twice the upper limit of normal for age. In patients with preexisting liver disease, \geq twofold elevation over the baseline level
	4. Adult respiratory distress syndrome defined by acute onset of diffuse pulmonary infiltrates and hypoxemia in the absence of cardiac failure, or evidence of diffuse capillary leak manifested by acute onset of generalized edema, or pleural or peritoneal effusions with hypoalbuminemia
	5. A generalized erythematous macular rash that may desquamate
	6. Soft-tissue necrosis, including necrotizing fasciitis or myositis, or gangrene

An illness fulfilling criteria IA and II can be defined as a definite case. An illness fulfilling criteria IB and II can be defined as a probable case.

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fulminant and to progress rapidly. Therefore, early suspicion and recognition of the infection is emphasized. Treatment mainly consists of appropriate antibiotics, early surgery when required and intravenous administration of immunoglobulins in STSS cases.

Antibiotics

Antibiotics are still the cornerstone of treatment for severe GAS infections. Penicillin, clindamycin and erythromycin are the antimicrobials of choice. Penicillin remains very active against streptococci, and resistance is not a problem. However, in 1952 Eagle³⁵ described an interesting phenomenon, which bears his name today.³⁶ In severe infections in which large numbers of bacteria are found, expression of penicillin-binding proteins is decreased, and therefore penicillin efficacy is diminished. In experimental models of myositis, it has been shown that antibiotics acting as protein synthesis inhibitors (e.g., lincosamides, macrolides) are more active,^{35,36} the hypothesis being the suppression by the antibiotic of the bacterial production of the M protein or the SPEs. Clindamycin was shown to be the most efficient antibiotic available for several reasons. It is not affected by the inoculum size, it facilitates GAS phagocytosis by inhibiting M-protein synthesis, it suppresses the production of bacterial toxins and it has a longer post-antibiotic effect than β lactams.³⁷

Erythromycin, on the other hand, has been shown to be less active than clindamycin but better than penicillin in an experimental model.³⁶ The erythromycin resistance rate in North America is about 4% but may be higher in other countries, reaching, for example, 72% in Japan.¹¹ This implies that clindamycin should be administered in cases of severe GAS infections and must be the alternative

medication to erythromycin in patients allergic to β lactams.

No study has clearly evaluated the efficacy of combination therapy for severe streptococcal infections, but because of the severity of the problem, this practice has been advocated.³⁸ The most suitable combination, because of different action mechanisms, consists of penicillin and clindamycin, administered together.

Surgery

Early surgical intervention is a life-saving procedure in the context of severe infections. Surgical drainage, fasciotomy or even amputation are always indicated in necrotizing fasciitis or myositis. Often, the definitive diagnosis will be made in the operating room, when all the anatomic stuctures are visualized. Physicians in surgical practice should be alert to the possibility of GAS infections and act accordingly by operating without delay when there is a suspicion of necrotizing fasciitis or myositis. Later in the course of the disease, surgical intervention may become risky because of toxicity or disease progression to areas where débridement is difficult, such as the face and thorax.

Hyperbaric oxygen therapy has been advocated in GAS myositis by analogy with clostridial muscle infections, but this concept is merely anecdotal.¹³

Intravenously administered immunoglobulins

The superantigen theory has led some to investigate the value of intravenous administration of human immunoglobulins (IVIG) in the management of severe streptococcal infections.²⁰ A recent clinical and laboratory case-control study involving patients with STSS has clearly demonstrated a significant drop of the death

rate in the IVIG-treated group compared with the control group (40% v. 80%).³⁹ This study also showed an effective superantigen-neutralizing activity related to IVIG administration in STSS patients.⁴⁰ The current dosage recommended for IVIG is 2 g/kg daily for 2 days.

This promising avenue is gaining in importance and is becoming a widely accepted practice in Canada for cases meeting STSS criteria. It is worthwhile noting that immunoglobulins must not be administered to patients with IgA-deficiency and those having circulating anti-IgA antibodies. Side effects (dizziness, nausea, chills and dyspnea) are rare (less than 5%) and usually minor.

Prophylaxis in cases of close contact

There are no firm recommendations regarding the management and antibiotic prophylaxis for contacts of patients with GAS invasive infections. Nevertheless, secondary cases of invasive GAS infections, sometimes occurring as household clusters, have been reported.^{33,41,42} Prophylaxis has been advocated by several groups including ours. We are conducting a study on the carriage rate of GAS in contacts of patients with invasive infections. Our data show that about 27% of contacts who spent more than a total of 24 hours with the index case in the week preceding the start of the illness, carry the same GAS strain. In the group having between 12 and 24 hours' contact, only 1.8% of the patients were found to harbour the bacteria.⁴³ This suggests that antibiotic prophylaxis should likely target only cases of prolonged contact. We give a 10-day course of treatment consisting of a cephalosporin (e.g., cephalexin), or erythromycin in allergic patients. Shorter courses of antibiotics (4 days)

have been shown to be ineffective, especially when rifampin is used, so rifampin should not be administered in these cases.⁴⁴

CONCLUSIONS

Because surgery plays a key role in the management of GAS invasive infections, surgeons should be aware of the multiple clinical aspects of the disease. Early recognition of potential GAS infections is essential, as survival depends on rapid initiation of appropriate treatment. Antibiotics, surgery, and probably intravenous administration of human immunoglobulins are all indicated in cases of severe infection. In spite of modern therapy, the death rate remains high, and new therapeutic alternatives have to be found in order to reduce this rate.

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