Necrotizing fasciitis secondary to Group A streptococcus

Morbidity and mortality still high

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abstract

OBJECTIVE To update physicians on Group A streptococcal necrotizing fasciitis, including current methods of diagnosis and treatment.

QUALITY OF EVIDENCE Current literature (1990-1998) was searched via MEDLINE using the MeSH headings necrotizing fasciitis, toxic shock syndrome, and *Streptococcus*. Articles were selected based on clinical relevance and design. Most were case reports, case series, or population-based surveys. There were no randomized controlled trials.

MAIN MESSAGE The hallmark of clinical diagnosis of necrotizing fasciitis is pain out of proportion to physical findings. Suspicion of underlying soft tissue infection should prompt urgent surgical examination. Therapy consists of definitive excisional surgical débridement in conjunction with high-dose intravenous penicillin G and clindamicin. Risk factors for mortality include advanced age, underlying illness, hypotension, and bacteremia.

CONCLUSION Necrotizing soft tissue infections due to Group A streptococcus might be increasing in frequency and aggression. Overall mortality remains high (20% to 34% in larger series). Clinical diagnosis requires a high level of suspicion and should prompt urgent surgical referral.

résumé

OBJECTIF Présenter aux médecins l'information la plus récente concernant les fasciites nécrosantes à streptocoques du groupe A, notamment les méthodes actuelles de diagnostic et de traitement.

QUALITÉ DES DONNÉES Une recension des ouvrages récents (1990-1998) a été effectuée dans MEDLINE à l'aide des titres MeSH en anglais pour fasciite nécrosante, syndrome de choc toxique et *Streptococcus*. Le choix des articles se fondait sur la conception et la pertinence clinique. La plupart d'entre eux portaient sur des rapports de cas, des séries de cas ou des enquêtes fondées sur la population. Il n'y avait aucun essai aléatoire contrôlé.

PRINCIPAL MESSAGE La caractéristique singulière du diagnostic clinique de la fasciite nécrosante se situe dans la douleur hors de proportion par rapport aux observations physiques. Quand une infection sous-jacente des tissus mous est suspectée, il faut sans délai procéder à un examen chirurgical. La thérapie consiste en une excision chirurgicale définitive, de concert avec l'administration de pénicilline G et de clindamycine à fortes doses par voie intraveineuse. Au nombre des facteurs de risque de mortalité figurent un âge avancé, une maladie sous-jacente, l'hypotension et la bactériémie.

CONCLUSION Les infections nécrosantes des tissus mous causées par les streptocoques du groupe A pourraient s'accroître en fréquence et en gravité. La mortalité globale demeure élevée (20% à 34% dans les séries plus importantes). Le diagnostic clinique exige d'être fortement aux aguets et devrait inciter à un aiguillage d'urgence en chirurgie.

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Occurrences of aggressive necrotizing soft tissue infections have been documented for centuries. Hippocrates described this entity and has been quoted:

> [M]any were attacked by the erysipelas, … suffered from severe inflammations, and the erysipelas would quickly spread widely.… Flesh, sinews, and bones fell away in large quantities.… There were copious fluxes; … there were many deaths.[1]

A perception reflected in the lay press and medical literature holds that the frequency of these infections has increased recently,[2] although statistics might be incomplete and could vary between geographic areas because of differences in surveillance methods.

This paper illustrates the evolution of streptococcal necrotizing fasciitis (NF) from limb swelling and signs of sepsis, through rapid progression of skin lesions to necrosis of deep tissues, and, in this case, death. Several features of Group A streptococcal (GAS) NF are described, most notably the predilection for subtle presentation followed by a dramatic and rapid course.

Although soft tissue infections can be caused by other bacteria, such as Gram-negative rods, clostridia, and mixed flora, this article focuses on current knowledge about diagnosis and treatment of necrotizing soft tissue infections secondary to GAS infection. Although clinical series have not demonstrated that early intervention affects clinical outcome, the rapid course of this illness illustrates the urgent need for prompt recognition and definitive management.

Quality of evidence

A MEDLINE search from 1990 to 1998 was conducted using the MeSH headings necrotizing fasciitis, toxic shock syndrome, and *Streptococcus*. The search was limited to English-language articles. Papers discussing epidemiology, pathophysiology, diagnosis, and management were selected based on clinical relevance. The bibliographies of these articles were used to identify additional papers. Articles reviewed include mainly case reports and case series, as well as a few population-based surveys. No randomized clinical trials were available.

Recommendations of the Working Group on Severe Streptococcal Infections[2] were considered, as well as those of the Ontario Group A Streptococcal Study Group.[3,4]

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Case description

A 74-year-old woman was referred from an emergency department to a medical service for bilateral leg swelling and discomfort of 8 hours' duration, refractory to diuretic therapy. On presentation, the patient's complaints were nonspecific; her main concern was the swelling and inability to move either leg because of discomfort. She denied having fever, chills, nausea, vomiting, diarrhea, myalgias, or headache.

The patient's medical history included a gastric malignancy and pulmonary hypertension secondary to bronchiectasis. On examination, she was frail and uncomfortable. Heart rate was 110 beats per minute, respiratory rate was 16 breaths per minute, and blood pressure was 90/60 mm Hg supine. Jugular venous pressure was below the sternal angle. Temperature was 37.8°C. Her neck was supple, with no lymphadenopathy. There was a loud S_2 and a systolic ejection murmur at the lower left sternal border. All pulses were palpable and equal, including posterior tibial, dorsalis pedis, and popliteal bilaterally.

Pitting edema was present bilaterally and extended to the umbilicus. The legs were moderately tender to palpation. A 4 × 4-cm area of slight dusky discoloration was present on her medial left shin, which initially had the appearance of a bruise.

White blood cell count was 17.7×10^9/L. Hemoglobin was 11.3 g/dL; platelets were 240×10^9/L. Electrolytes, renal function, and glucose measurements were normal. Creatinine level was normal at 88 μmol/L. Liver function tests included a γ-glutamyl transpeptidase level of 364 U/L, alkaline phosphatase of 319 U/L, lactate dehydrogenase of 559 U/L, total bilirubin of 30 μmol/L, aspartate transaminase (AST) of 40 U/L, and alanine transaminase (ALT) of 36 U/L. Creatine kinase was less than 20 U/L. The prothrombin time (international normalized ratio, or INR) was initially 1.6, and later rose to 2.8. Fibrin degradation products were increased at 10 mg/L (<10).

A duplex ultrasound scan of her legs was negative for deep venous thrombosis. Plain x-ray films of her legs revealed no gas in the tissues. Chest radiography showed signs of pulmonary hypertension only. Electrocardiography showed strain in the inferior leads. Blood and urine samples were sent for culture. Treatment with broad-spectrum antibiotics (cefazolin) was begun along with aggressive infusion of intravenous crystalloid.

Over the next 2 hours, leg pain progressed and rapidly became excruciating, requiring intravenous narcotics. The patient remained in shock, with a systolic

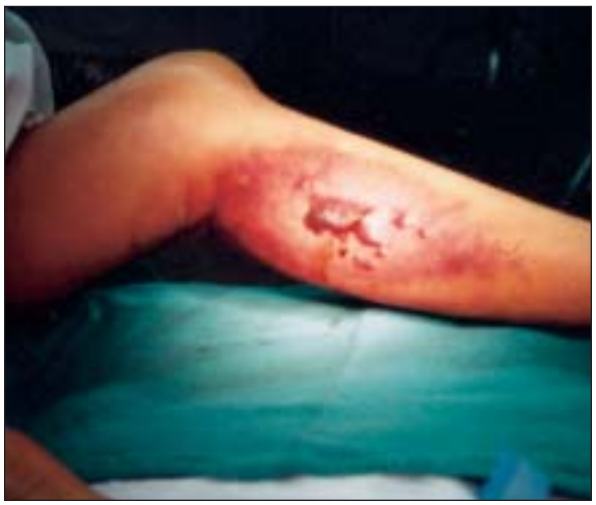

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Figure 1. **Bullae on left leg**

blood pressure of 70 to 80 mm Hg. The lesion on her left leg quadrupled in size, and bullae formed (**Figure 1**). Antibiotics were changed to high-dose penicillin G, 3 million units every 4 hours, and clindamicin, 900 mg every 8 hours.

The surgery service was consulted urgently for assessment and management of presumed NF. The patient was taken to the operating room 8 hours after presentation for examination under anesthesia and attempted débridement or amputation. By the time surgery was begun, however, the process was apparent in the contralateral (right) thigh (**Figure 2**). Examination revealed extensive tissue necrosis and destruction of the fascia to above the inguinal ligament; thus the case was not amenable to surgical management. The patient died the following day, 30 hours after presentation to the emergency department. Blood cultures drawn on presentation were positive for GAS.

Definitions and epidemiology

Streptococcal soft tissue infections are defined by the layer of tissue involved.[5] Infections can range from pyoderma and cellulitis through NF and myositis.

Streptococcal toxic shock syndrome (STSS) can be associated with invasive infections secondary to GAS infection. It is clinically similar to toxic shock syndrome (TSS) induced by toxin-producing strains of *Staphylococcus aureus*. Streptococcal toxic shock syndrome includes isolation of GAS from a sterile site, plus clinical signs of severity. These include hypotension and two or more signs of renal impairment, coagulopathy, hepatic involvement, adult respiratory distress syndrome, generalized rash, or soft-tissue necrosis.[5,6]

Necrotizing fasciitis is a clinical and histologic diagnosis; the condition can be caused by GAS or other organisms. The focus of this paper is NF secondary to GAS infection.

Epidemiology appears to differ by geographic region, although this might be a function of surveillance and reporting methods, and possibly of demographics. Two recent papers describing the epidemiology of invasive GAS infections are from the United States and Ontario.

In the United States, 10 000 to 15 000 cases of invasive streptococcal infections are reported annually; 5% to 10% involve NF, and 30% mortality overall is reported for invasive infections.[7] A retrospective survey of 128 patients was done in Arizona by identifying GAS from microbiology records and abstracting information from the appropriate medical records. This study covered April 1985 to March 1990. Annual

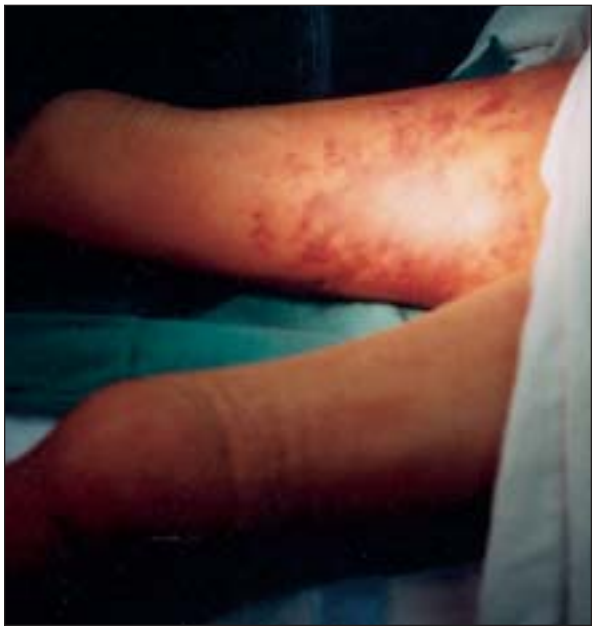

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Figure 2. **Infection spread to contralateral thigh before surgery began**

age-adjusted incidence was 4.3 invasive infections per 100 000 population.

Incidence varies significantly with age and ethnicity; however, the US incidence is 10 times the baseline incidence among Native Americans.[8] Invasive infections are more likely to occur and to be fatal in patients at extremes of age (P =.006 for older patients, age not defined; P =.002 for patients 5 years or younger). Similarly, invasive infections are more likely in patients with such underlying illnesses as diabetes (43% vs 14%, P =.002) or alcoholism complicated by cirrhosis (23% vs 3%, P =.001). Conversely,

TSS appears to occur in younger people (P =.02, age not specified), who were less likely to have underlying medical conditions (P =.008). Overall incidence of invasive infections and case mortality of 20% did not increase between 1985 and 1990, but the proportion of infections associated with hypotension, gastrointestinal and renal conditions, rash, and desquamation did increase significantly (P < .02 for each feature).

Similarly, a study of invasive streptococcal infections in England and Wales showed a stable incidence from 1992 to 1994,[9] with 200, 212, and 200 blood isolates in the first 6 weeks of 1992, 1993, and 1994, respectively. In Norway, the incidence of NF due to GAS was reported to increase between 1992 and 1994, with 13 cases reported, for an incidence of less than 2/100 000 annually, as opposed to none before 1992. However, this result has also been attributed to a possible change in surveillance methods.[10]

A study from Ontario used prospective surveillance methods to analyze incidence, features, outcome, and microbiologic characteristics over the period November 1991 to May 1995.[3] Patients meeting clinical and histopathologic criteria for streptococcal NF were included. Information was gained by chart review and patient or physician interview. This study showed an increase in the incidence of GAS NF, from 0.085 per 100 000 in 1991 to 0.4 per 100 000 in 1995 (P <.001), with a 34% case fatality rate. As surveillance methods were constant throughout the study period, this result is unlikely to be affected by methodologic errors.

In Ontario,[3] NF occurs more frequently in winter (61% from December to March, P <.001) and in men (0.25 vs 0.15 per 100 000, P =.003). Men are affected at a younger age than women (median age 49 vs 62, P =.002). Frequency increases with age (0.55 per 100 000 patients older than 65 vs 0.15 per 100 000 patients younger than 45, P <.001). Half of patients have a history of injury to the skin, while an additional quarter have a history of blunt trauma. Seventy-one percent of cases occur in people with one or more chronic illnesses. Half occur in one lower limb; an additional third occur in one upper limb.

Risk factors

Risk factors for mortality in Ontario include age older than 65 years (relative risk [RR] 3.86, 95% confidence interval [CI] 1.84-8.09, P <.001; 61% older than 65, 27% 35 to 64, 0% younger than 35), chronic illness (RR 2.95, CI 1.13-7.71, P =.01), hypotension (RR 12.0, CI 3.0-4.60, P <.001), coagulopathy (RR 2.23, CI 1.13-4.23, P =.03), bacteremia (RR 3.09, CI 1.75-5.44, P <.001), acute renal failure (RR 2.90, CI 1.12-4.20, P =.03), and liver abnormalities (AST or ALT greater than twice the upper limit of normal or twice baseline, RR 2.17, CI 1.12-4.20, P =.005). Patients with TSS in addition to NF had a 67% mortality rate, in contrast to a 5% mortality rate among those with NF alone (P <.001). Multivariate analysis showed age, hypotension, and bacteremia to be independently associated with mortality. There was a trend toward better survival with therapy that included clindamicin (RR 0.55, CI 0.23-1.02, P =.06). Factors that were not significant included skin break, acute respiratory distress syndrome, serotype, toxin type, or therapy that included intravenous γ-globulins.

Use of nonsteroidal anti-inflammatory drugs (NSAIDS) has been suggested to contribute to the rapidity with which NF due to GAS progresses. The postulated mechanism of action is inhibition of neutrophil chemotaxis, phagocytosis, and bactericidal activity, which have been demonstrated in vitro against other Gram-positive cocci, including another strain of *Streptococcus*.[11] The data conflict, however, and this observation has also been attributed to an initial masking of symptoms by NSAID use.[5]

In a case series from France, five of seven cases seen between 1983 and 1985 (four of which grew GAS) had a fulminant course.[11] All five had been treated with NSAIDS after diagnosis, with an acceleration in evolution of the disease process. Three patients died. All patients had received intravenous penicillin G at 15 to 25 million U daily and had undergone surgical débridement within 15 hours of presentation. In contrast, in Ontario, NSAID use in 11 patients was not associated with mortality, development of STSS, or amputation.[3] The possible role of NSAIDS in disease progression thus remains unconfirmed.

Pathophysiology

Necrotizing fasciitis has been associated with the presence of streptococcal M proteins types 1 and 3,[12,13] exotoxins A and B, and mitogenic factor. These could stimulate a massive release of cytokines from immune cells and result in shock, organ failure, depression of myocardial function, and immune suppression. Proteinases and other enzymes might contribute to tissue destruction.[5]

Diagnosis and investigations

While subcutaneous soft tissue infections can present with nonspecific symptoms, the cardinal manifestation is pain out of proportion to physical findings.[3,5,8] The skin in some cases can be anesthetic, which

might be due to thrombosis of cutaneous nerves and is a late sign. Skin can be shiny and erythematous. Formation of bullae, dishwater-coloured discharge, and frank necrosis are probably secondary to thrombosis of underlying vessels. Cutaneous manifestations usually occur within 24 hours of onset of symptoms. Lymphadenitis and lymphangitis are rare.

Once a necrotizing subcutaneous soft tissue infection is suspected, the cornerstone of diagnosis is examination by surgical dissection. The characteristic feature of NF is easy separation of fascia from other tissues by blunt dissection, because of necrosis of fascia and subcutaneous tissue, with liquefaction. Muscle is usually spared, but myonecrosis could occur secondary to compartment syndrome. Infection can be confirmed by Gram's stain or frozen section of affected tissue. Blood and tissue should be sent for culture.

Microscopic examination of affected tissue reveals coagulation necrosis of superficial fascia, subcutaneous fat, and possibly deep fascia. Inflammatory infiltration, thrombosis of blood vessels, and necrosis of glands can be present.[6,12]

Adjunctive laboratory tests involve documentation of and monitoring for organ dysfunction, including renal and hepatic problems, coagulopathy, and creatine kinase. Plain radiographs are usually not helpful. Gas in the soft tissues is not characteristic of GAS, and if present, should raise suspicion of clostridial infection. Computed tomographic scanning[14] or magnetic resonance imaging[15] might localize and delineate the extent of tissue involvement. Many false-negative results occur with radiographic imaging, however, and surgical exploration should not be delayed.

Treatment

While antibiotics (including high-dose intravenous penicillin G and clindamicin) and supportive measures should be instituted immediately, definitive therapy must involve early excisional débridement or amputation of affected tissue.[16,17] In the Ontario study, 23% of survivors required amputation.[3]

High-dose penicillin G remains the antibiotic of choice for treatment of GAS, with no resistance recorded.[9] Some resistance to erythromycin, the agent of choice for penicillin-allergic patients with streptococcal pharyngitis, has been reported. In animal models, penicillin is less effective against aggressive infections, such as those with a large inoculum, because there is less expression of penicillin-binding proteins in the S or stationary phase of the bacterial cell cycle, and thus less of a target for antibiotic action.

Clindamicin acts by a direct inhibitory effect on protein synthesis, including exotoxin, thus slowing toxin-mediated destruction of soft tissue. In addition, it could slow the destructive effect of inflammatory cytokines on organ systems.

Intravenous immune globulins (ivIg) presumably bind streptococcal toxin and opsonize bacteria. While the utility of ivIg as an adjunctive agent in these infections has been reported, no prospective trials have related its use to clinical outcomes.[3,5,9] In Ontario, of 77 patients with GAS NF, 10 received ivIg as adjunctive therapy. There was one fatality in the ivIg group, versus 25 in the group that did not receive ivIg, for an RR of 0.27 (CI 0.04-1.80, P =.15). While no significant effect on survival was shown in this study, the numbers examined were small, and thus no definitive conclusions can be drawn.[3] Intravenous immune globulin is expensive and is not immediately available in many centres. Where available, it should probably be used cautiously until definitive data are available.

There have been some reports of using hyperbaric oxygen (HBO) for soft tissue infections. Data are mixed, however, and largely based on retrospective analyses.[18,19] For example, a study of 29 patients[18] showed that the 17 who received HBO in addition to antibiotics and surgical débridement had significantly lower mortality than those who did not (23% in the HBO group vs 66%, P <.02). This study, however, analyzed patients with NF secondary to several organisms, and there were large differences between groups in the numbers who grew *Streptococcus*, strain not specified (12/17 in the HBO group vs 2/12), and other organisms (5/17 *Clostridia* in the HBO group vs 8/12). Therefore, conclusions about using HBO for GAS NF are difficult to extrapolate from the data.

A second study, also retrospective, examined the role of adjunctive HBO in truncal NF among 54 patients treated over 12 years.[19] Despite significantly younger patients in the group that received HBO (51 years vs 61, P <.05), this study showed no difference in mortality between groups (30% in the HBO group vs 42%, P value not provided). This result is attributed by the authors to selection bias, because more critically ill patients were more likely to receive HBO. However, the data must be taken in the context of a minority of cases being positive for GAS (7/54, or 13%). Thus, while HBO is likely not harmful, its use should not delay definitive surgical débridement.

Finally, to our knowledge, no data on contact prophylaxis are specific to NF. This issue is discussed at length by the Ontario group.[3] Among 152 household contacts of patients with invasive GAS infections,

there was a 12% rate of colonization. Among 620 household contacts in a group in which 20/323, or 6.2%, of patients had NF, the disease rate was 3.2/1000 (CI 0.39 to 12/1000) for all invasive GAS. With additional contacts included, the risk was similar and was estimated to be 200 times the risk in the general population. This rate of disease risk and case fatality were estimated to be similar to contacts of patients with sporadic meningococcal infection.

The best approach to prophylaxis is unclear, as is the best method to estimate its effectiveness. In this case, on the advice of the Infectious Disease Service, strict hand washing was instituted among caregiving staff and family members. All contacts were counseled about signs and symptoms of infection and were advised to go directly to the emergency department immediately for full treatment should any signs or symptoms occur.

Conclusion

Although literature reports do not all agree, necrotizing soft tissue infections due to GAS appear to be increasing in incidence or aggression, at least in some areas. Documented predisposing factors and conditions include advanced age, chronic illness (such as diabetes mellitus and alcoholism), and male sex, as well as possibly underlying states of immune deficiency. Skin disease, such as chickenpox or other lesions, might also predispose patients to invasive infection. Clinical diagnosis rests on a high level of suspicion, triggered when pain is out of proportion to physical findings (usually in one limb), and supported by clinical and laboratory signs of severity and organ dysfunction.

Urgent surgical examination should be undertaken promptly. Treatment includes definitive surgical débridement in conjunction with high-dose intravenous penicillin G and high-dose clindamicin. Adjunctive treatment with ivIg and HBO are unproven therapies that could be considered in selected cases. Overall mortality remains high, from 20% to 34% in larger series (N ≥77 vs N ≤ 13), with increased mortality correlated to age, bacteremia, hypotension, and underlying disease.

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Key points

- Necrotizing fasciitis due to Group A streptococci appears to be increasing in frequency and severity in some geographic areas.
- Predisposing factors include older age, chronic disease, and being male.
- Clinical diagnosis depends on a high level of suspicion, especially with pain out of proportion to physical findings.
- Aggressive treatment should include surgical débridement with high doses of penicillin G and clindamycin.
- Overall mortality remains high: 20% to 34% in large series.

Points de repère

- La fasciite nécrosante causée par les streptocoques du groupe A semble s'accroître en fréquence et en gravité dans certaines régions géographiques.
- Les facteurs de prédisposition sont, entre autres, l'âge avancé, les maladies chroniques et le fait d'être de sexe masculin.
- Le diagnostic clinique requiert d'être fortement aux aguets, en particulier en présence d'une douleur hors de proportion par rapport aux observations physiques.
- Un traitement vigoureux doit comporter une excision chirurgicale et de fortes doses de pénicilline G et de clindamycine.
- La mortalité globale demeure élevée: de 20% à 34% dans les séries d'importance.

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