

Toxic Shock Syndrome

Major Advances in Pathogenesis, But Not Treatment

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KEYWORDS

- Toxic shock syndrome • *Staphylococcus aureus* • Group A streptococcus
- Necrotizing fasciitis • Superantigen • Cytokine storm

KEY POINTS

- Although the incidence of menstrual staphylococcal toxic shock syndrome (TSS) declined sharply in the 1990s, the incidence of both menstrual and nonmenstrual cases has remained stable over the last decade, at about 0.3 to 0.5 cases per 100,000 population.
- The incidence of streptococcal TSS (STSS) increased dramatically in the mid-1980s, but has since remained relatively stable since at 2 to 4 per 100,000 population.
- Both staphylococcal TSS and STSS are principally superantigen-mediated diseases; however, staphylococcal TSS is secondary to a localized infection, whereas STSS is the result of an invasive infection.
- Both in vitro and in vivo data support the potential role of intravenous immunoglobulin for the treatment of STSS and possibly necrotizing fasciitis (NF).
- The recommendation of immediate radical excision of necrotic tissue in patients with STSS NF is not supported by clinical studies and should be reconsidered.

BACKGROUND

Staphylococcus aureus and *Streptococcus pyogenes* (group A streptococci) are gram-positive pathogens capable of producing a variety of bacterial exotoxins, including a family of toxins known as superantigens (SAGs). SAGs interact with antigen-presenting cells (APCs) and T cells to induce T-cell proliferation and massive cytokine production, which leads to fever, rash, capillary leak, and subsequent hypotension, the major symptoms of toxic shock syndrome (TSS) (**Fig. 1**).¹

A syndrome of fever, myalgias, sore throat, edema, scarlatiniform rash, and desquamation associated with *Staphylococcus aureus* infection was first described in 1927, and in 1978, by Todd and colleagues^{2,3} who coined the term staphylococcal TSS. By Stevens² in 1980, young menstruating women using high-absorbency tampons were identified as a high-risk group, with cases also observed in men and nonmenstruating

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Crit Care Clin 29 (2013) 651–675
<http://dx.doi.org/10.1016/j.ccc.2013.03.012>

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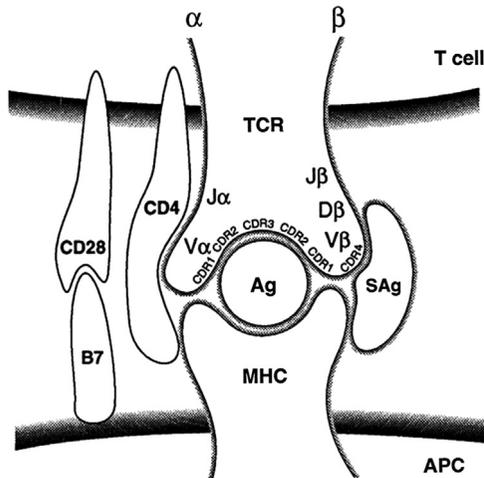


Fig. 1. Bridging of T cells and APCs: schematic model of SAgs. SAgs interaction with T-cell receptor and class II molecules. (From Kotb M. Bacterial pyrogenic exotoxins as superantigens. *Clin Microbiol Rev* 1995;8:412; with permission.)

women.^{4,5} As the pathogenesis was better understood, it became clear that *Staphylococcus aureus* toxins, called SAgs, in conjunction with host susceptibility for the development of TSS.^{6,7}

In 1987, Cone and colleagues⁸ described 2 patients with severe group A streptococcal (GAS) infections having clinical features similar to staphylococcal TSS. This syndrome, designated the streptococcal toxic shock-like syndrome (STSS),⁹ was characterized by Stevens and colleagues¹⁰ in a series of 20 patients. Most patients were less than 50 years old and otherwise healthy. All had invasive GAS infections characterized by signs including shock, multiorgan system involvement, and rapidly progressive, destructive soft tissue infection (necrotizing fasciitis [NF]). The case fatality rate was 30%, even although most patients received appropriate antimicrobial therapy, supportive care, and, where necessary, surgical debridement. M types 1 and 3 were the most common type, and 80% of the isolates produced pyrogenic exotoxin A. Initially, NF was recognized as a component of STSS, and was included as part of diagnostic criteria for STSS.¹¹ However, it is now recognized as a separate entity. It is defined as GAS infection of the subcutaneous tissue and fascia that results in necrosis with relative sparing of the underlying muscle.

Over the last decade, much has been learned about the pathogenesis of TSS: the role of SAgs, GAS M proteins, and the large numbers of other secreted virulence factors, including cytolytins. This new information must make us rethink the past dogma regarding the management of this important disease, both medically and surgically.

EPIDEMIOLOGY

The case definitions for staphylococcal TSS and STSS are presented in **Table 1**.

Staphylococcal TSS

The incidence of staphylococcal TSS increased sharply in the 1980s. These cases occurred most commonly in young white women.¹² Clinical illness arose during menstrual periods and was associated with the use of highly absorbent tampons. Although

Criteria	TSS	
	<i>Staphylococcus aureus</i>	GAS
Isolation of organism		
Nonsterile site		✓
Sterile site		✓
Fever	✓	
Hypotension	✓	✓
Rash	✓	
Skin desquamation	✓	
Multisystem involvement		
≥2 of following		✓
≥3 of following	✓	
Gastrointestinal	✓	
Muscular	✓	
Mucous membranes	✓	
Renal	✓	✓
Hepatic	✓	✓
Hematologic	✓	✓
Central nervous	✓	
Liver	✓	✓
Respiratory		✓
Soft tissue necrosis		✓
Rash		✓

Data from Wharton M, Chorba TL, Vogt RL, et al. Case definitions for public health surveillance. *MMWR Recomm Rep* 1990;39:1–43; and Breiman RF, Davis JP, Facklam RR, et al. Defining the group A streptococcal toxic shock syndrome: rationale and consensus definition. *JAMA* 1993;269:390–1.

the incidence of TSS sharply declined after the withdrawal of some brands of tampons, a slight increase in incidence of all TSS cases has occurred since 2000. In 1 report from Minnesota, the incidence increased from 0.8 per 100,000 in 2000 to 3.4 per 100,000 in 2003.¹³ A subsequent study from Minnesota identified 61 cases of TSS between 2004 and 2006.¹⁴ Among the 61 TSS cases, the median age was 21 years. There were 33 menstrual and 28 nonmenstrual TSS cases, with menstrual cases trending toward younger age and fewer preexisting conditions. There were minimal differences in clinical presentation between menstrual and nonmenstrual cases. Of the 28 nonmenstrual cases, 13 had a skin or soft tissue infection, of which 4 were postsurgical. In addition, 10 had no primary source identified.

Association with methicillin-resistant *Staphylococcus aureus*

Methicillin-resistant *Staphylococcus aureus* (MRSA) strains can produce TSS toxin 1 (TSST-1), and patients infected with these strains may develop TSS. In a series of 30 patients with TSST-1-positive MRSA infections from France and Switzerland, 5 had TSS, 9 had possible TSS (fever and a rash without shock), 2 had neonatal TSS-like exanthematous disease, 1 had scarlet fever, and the rest had other infections.¹⁵ Nine of 30 cases were community acquired and the rest were hospital acquired or had an unknown site of acquisition. In the study reported from Minnesota,¹⁴ 4 cases (7%) had *Staphylococcus aureus* isolates that were MRSA (1 menstrual, 3 nonmenstrual).

Two MRSA isolates, both from nonmenstrual cases, had antimicrobial susceptibility patterns suggestive of community-associated MRSA.

Association with influenza

MacDonald and colleagues¹¹ in 1987 described 9 cases of severe hypotension or death compatible with TSS in Minnesota as a complication of influenza and influenza-like illness; 5 of the patients died. During this time, an influenza outbreak was occurring in the state. Cultures of respiratory secretions were performed in 8 patients; *Staphylococcus aureus* was isolated from all of them. During the influenza pandemic of 2009, a study including 35 adult US intensive care units (ICUs) over the course of 1 year identified 683 critically ill adults with confirmed or probable H1N1.¹⁶ Within 72 hours of ICU admission, 207 (30.3%) cases had a presumed bacterial coinfection identified. *Staphylococcus aureus* (n = 57) was the most common pathogen. Bacterial coinfection, especially with *Staphylococcus aureus*, was associated with a significant increment in morbidity and mortality.

STSS

The epidemiology of GAS diseases has changed dramatically over the course of the past few centuries. Historical literature describes epidemics of scarlet fever, which presented with fulminant sepsis and high mortality.¹⁷ Scarlet fever became less common in the industrialized world during the middle part of the twentieth century, before the advent and availability of antibiotics, possibly because of improvements in living conditions, nutrition, or pathogenicity of circulating GAS strains.

Periodic upsurges in the incidence of invasive GAS infections began to be reported worldwide in the 1980s.^{5,18–20} The incidence rates of invasive GAS disease now show remarkable consistency between industrialized nations, with rates between 2 and 4 per 100,000.²¹ Incidence of invasive GAS infection is typically higher in winter and spring and lowest in autumn.⁵ The rates of invasive GAS disease are several-fold higher in developing countries (>10 per 100,000) in keeping with the observation of a high burden of other GAS diseases in these areas. A review of global data in 2005 estimated that 97% of the cases and deaths caused by invasive GAS disease occur in developing countries.²² Case fatality rates in both affluent and resource-poor countries approach 50% in the presence of STSS.²³

A prospective population-based surveillance study for invasive GAS infections in Ontario from 1991 to 1995 identified 323 patients with invasive GAS disease, corresponding to an annual incidence of 1.4/100,000 population.⁵ The most common clinical presentations were soft tissue infection (48%), bacteremia with no septic focus (14%), and pneumonia (11%). NF occurred in 6% of patients, and STSS in 13%. The mortality was 15% overall, and 81% among those with STSS. Almost half of the pediatric cases of NF occurred in children with varicella. The strongest predictor of mortality associated with NF was patient age. Patients younger than 35 years had significantly lower mortality (0%) compared with mortality in those older than 70 years (65%). Bacteremia in patients with NF was significantly and independently associated with a greater risk of mortality. The increased incidence of this infection in Ontario was associated with shifts in the strains of GAS; M1 and M3 strains accounted for most cases. The number of cases of STSS in the greater Toronto/Peel region in Ontario has remained stable during the last decade (Fig. 2).

M types

M proteins are cell-surface-attached proteins that are composed of 2 polypeptide chains that form an α -helical coiled-coil configuration; they provide the basis of widely

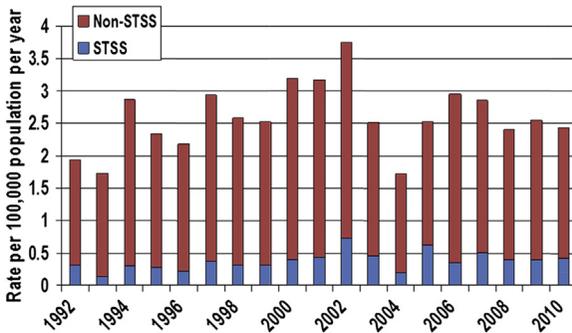


Fig. 2. From January 1, 1992 to December 31, 2010, a prospective, population-based, surveillance study of all invasive GAS infections in Metropolitan Toronto/Peel region, Ontario, Canada was performed. All microbiology laboratories serving Ontario hospitals telephoned the study office when GAS was isolated from specimens recovered from sterile sites. (Data from McGeer A. The Toronto Invasive Bacterial Disease Network. Available at: <http://tibdn.ca/data-publications/data/groupa/groupa-streptococcus-disease>. Accessed May, 2013.)

used epidemiologic typing schemes that use serologic methods (M type) or nucleotide sequence analysis of the M protein gene (*emm* type) (Fig. 3). Epidemiologic studies have revealed that certain disease manifestations are commonly associated with particular M types, such as M1 and M3 types, which are associated with the severe invasive manifestations STSS and NF.^{10,24,25} However, the outcome of infection depends not only on bacterial factors but also on host factors.²⁶ Whereas most GAS serotypes traditionally show cyclic epidemiologic patterns, appearing and disappearing from the community at different times, a genetically distinct serotype M1 clone, apparently more fit than other serotype M1 isolates, emerged during the mid-1980s and rapidly rose to dominance among disease isolates.^{24,27}

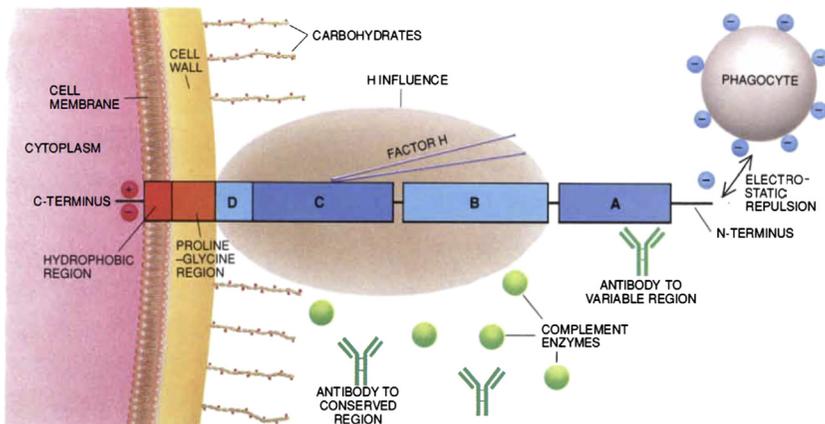


Fig. 3. Thwarting the immune system is the primary job of the M protein. Negative charges at the N terminus may repel phagocytic white blood cells. By binding with factor H—a regulatory protein produced by the human host, the M protein protects its most conserved regions from antibodies and complement enzymes. Only antibodies against the antigenically shifting hypervariable region can clear an established streptococcal infection from the body of the host. (From Fischett VA. Streptococcal M protein. *Sci Am* 1991;264:65; with permission from Tomo Narashima.)

CLINICAL***Staphylococcal TSS***

Staphylococcal TSS is separated into 2 major categories: menstrual and nonmenstrual illness.²⁸ Staphylococcal TSS also occurs in children. Patients younger than 2 years account for approximately half of the cases, and 62% have a history of preceding cutaneous nonsurgical lesions. Hajjeh and colleagues²⁹ found that cutaneous nonsurgical lesions were more common among children than other patients with nonmenstrual TSS.

Menstrual cases

Menstrual TSS, as its name implies, occurs during or within 2 days of women's menstrual periods, and the illness is most often associated with tampon use; the tampon association primarily results from tampon-introduced oxygen being required for TSST-1 production. The human vagina in the absence of tampons is normally anaerobic. TSST-1 is the cause of nearly all menstrual cases of TSS, likely because of its greater capacity than other SAGs to penetrate mucosal surfaces.

The withdrawal of highly absorbent tampons and polyacrylate rayon-containing products from the market partially explains the decrease in menstrual cases; however, tampon use remains a risk factor for TSS.³⁰ Women who develop TSS are more likely to have used tampons with higher absorbencies, used tampons continuously for more days of their cycle, and kept a single tampon in place for longer. The case fatality rate has declined for menstrual TSS from 5.5% in 1979 to 1980 to 1.8% in 1987 to 1996.²⁹

Nonmenstrual

Approximately one-half of reported TSS cases are nonmenstrual. Nonmenstrual TSS has been seen in a variety of clinical situations, including surgical and postpartum wound infections, mastitis, septorhinoplasty, sinusitis, osteomyelitis, arthritis, burns, cutaneous and subcutaneous lesions (especially of the extremities, perianal area, and axillae), and respiratory infections after influenza. The case fatality rate for nonmenstrual TSS is 5%.²⁹ In contrast to the menstrual cases, this rate has not decreased over time.

STSS

STSS may occur with infection at any site, but most often occurs in association with infection of a cutaneous lesion. Many invasive streptococcal infections have no known portal of entry.^{10,31} Transient bacteremia originating from the oropharynx has been suggested as the source in such cases. Signs of toxicity and a rapidly progressive clinical course are characteristic and the case fatality rate may exceed 50%.

NF

NF may follow local blunt or penetrating trauma to the skin. It occurs most commonly in the lower limb, followed by the upper limb.³² In adults, NF can be associated with intravenous drug use, whereas in children, varicella is a common precipitant.³³ Patients with GAS-associated NF may have only subtle signs of severity at initial presentation and can therefore be difficult to differentiate from a simple cellulitis. Severe pain and tenderness that is disproportionate to the physical findings are the clinical hallmark that differentiates NF from more superficial infection. Tense edema and the development of bullae that seem bluish as the disease progresses are also useful signs, but are often late signs and indicate significant tissue necrosis. Several studies have reported that patients with NF often have a history of recent blunt trauma.³⁴ A case control study confirmed that patients with NF were 6 times more likely than control individuals to have had a recent blunt trauma.³⁵ A potential mechanism was

provided by Bryant and colleagues,³⁶ who reported that skeletal muscle injury resulted in increased cellular vimentin expression, which enhanced binding of GAS to skeletal muscle cells.

The case fatality rate of GAS-associated NF is 30% to 50%, and most deaths occur in the first 48 hours after presentation, reflecting the rapidly progressive nature of the disease.³³ Between 30% and 50% of patients with GAS-associated NF develop STSS.

Community-acquired pneumonia

In the preantibiotic era, GAS was the cause in 3% to 5% of cases of community-acquired pneumonia, occurring most commonly after outbreaks of viral illness such as influenza or measles. Local complications such as empyema were common, and the reported case fatality rate was as high as 50%. Since the 1940s, the incidence of GAS pneumonia declined dramatically. However, the occurrence of pneumonia has increased with the resurgence of invasive GAS disease during the last several decades, with 10% of patients with invasive GAS disease presenting with pneumonia. Small outbreaks of GAS pneumonia have been described in chronic care facilities and within families, as well as sporadic cases occurring in the community. A Canadian population-based surveillance program of invasive GAS disease confirmed that GAS pneumonia is a severe illness of sudden onset frequently associated with local and systemic complications, particularly empyema (19%), STSS (32%), and death (38%).³⁷

DIAGNOSIS

Staphylococcal TSS

The diagnosis is primarily a clinical one, because there is no confirmatory diagnostic test (see **Table 1**). In contrast to STSS, *Staphylococcus aureus* is only rarely (5%) recovered from blood cultures.

STSS and STSS NF

The first criterion for defining STSS is the isolation of GAS in a patient with severe sepsis (see **Table 1**). GAS NF is rapidly progressive over a course of 1 to 4 days.³⁴ In the infected deep soft tissue, there is marked necrosis, acute inflammatory cell infiltration, and bacterial organisms, which are primarily concentrated along the major fascial planes. In necrotizing myositis, pathologic examination of the involved muscle typically reveals muscle necrosis with gram-positive cocci in chains seen between the muscle bundles. GAS is readily cultured from tissue samples from patients with NF, myositis, or severe cellulitis, in contrast to erysipelas biopsy specimens, from which streptococci only rarely can be cultured. An association between severity of tissue infection and bacterial load was shown by Thulin and colleagues,³⁸ who analyzed snap-frozen tissue biopsy specimens collected from patients with NF or severe cellulitis caused by GAS of varying serotypes. Bacteria were detected in all biopsy specimens, even those collected from distal areas. Biopsy specimens obtained as late as 20 days after diagnosis of infection and initiation of intravenous antibiotics still contained bacteria,³⁸ Bacteremia is common; 1 report showed that 88% of cases had positive blood cultures when obtained.³¹ There are some reports of the usefulness of magnetic resonance imaging: although sensitive, the imaging technique lacks specificity.^{39,40} The use of frozen-section biopsy specimens of suspected areas of tissue may enable early recognition of NF; however, the expertise to process and interpret biopsy specimens is not readily available in most clinical settings where and when patients present.⁴¹

Clinical features suggestive of STSS NF: (1) severe, constant pain; (2) bullae; (3) skin necrosis or ecchymosis (bruising), which precedes skin necrosis; (4) edema that extends beyond the margin of erythema; (5) cutaneous anesthesia; (6) systemic toxicity; and (7) rapid spread.⁴²

PATHOGENESIS

Staphylococcal Versus STSS

Although both staphylococcal TSS and STSS are principally SAg-mediated diseases, staphylococcal TSS is secondary to a localized infection, whereas STSS is the result of an invasive episode of streptococcal disease that may include bacteremia, cellulitis, NF, or myonecrosis. In addition to the production of SAGs, the GAS M proteins are responsible for releasing other virulence factors, including heparin-binding protein (HBP) and resistin (Fig. 4).

Cytokine Storm

Cytokines are signaling peptides, proteins, or glycoproteins, which are secreted by many cell types, including immune, epithelial, endothelial, and smooth muscle cells. They either enhance or inhibit inflammation in response to pathogens, nonself molecules, and toxins. If the interactions that lead to cytokine production are destabilized, a cytokine storm (or hypercytokinemia) can result, producing unbridled inflammation

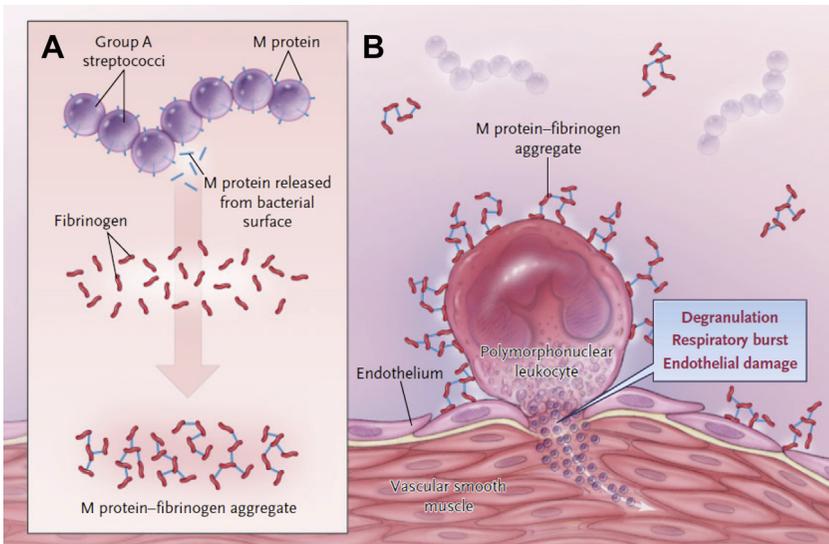


Fig. 4. Mechanism of damage caused by M protein. As GAS invades the blood, M protein is shed from its surface and forms a complex with fibrinogen. A recent study shows that the M protein-fibrinogen complexes bind to integrins on the surface of polymorphonuclear leukocytes, activating these cells. Once activated, the polymorphonuclear leukocytes adhere to endothelium and degranulate, releasing a wide variety of hydrolytic enzymes and producing a respiratory burst. The resulting damage to the underlying endothelium leads to vascular leakage and hypercoagulability, which in turn cause the hypotension, disseminated intravascular coagulation, and organ damage that are characteristic of STSS. (From Brown EJ. The molecular basis of streptococcal toxic shock syndrome. *N Engl J Med* 2004;350:2094; with permission.)

within tissues and key organs. TSS is believed to be the manifestation of a cytokine storm: the result of massive T-cell stimulation. Conventionally, T cells need 2 signals to become fully activated. Physiologically, the first signal arises from the interaction of T-cell receptor (TCR) molecules with peptide/major histocompatibility complex (MHC) complexes on APCs. The second signal is provided by the engagement of a so-called costimulatory receptor. The first to be discovered and still the most prominent of these costimulatory receptors is CD28 (see **Fig. 1**). There are 2 mechanisms by which T cells can be superstimulated to result in a cytokine storm: SAGs, the major cause of TSS; and superagonistic CD28 specific antibodies.

SAGs

Nearly all *Staphylococcus aureus* strains have the capacity to produce 1 or more SAG proteins, including TSST-1 and staphylococcal enterotoxins serotypes A, B, C, D, E, and I.⁴³

GAS also produces numerous SAGs, including streptococcal pyrogenic exotoxin serotypes A, C, G-M, and streptococcal mitogenic exotoxin Z.⁴³ Although originally described in *Staphylococcus aureus* and GAS, SAGs are increasingly being isolated from coagulase-negative staphylococci and other groups of β -hemolytic streptococci, particularly groups C and G.⁴³

SAGs bypass normal mechanisms regulating antigen presentation and processing, in which peptide fragments are presented to the T cell via a specific peptide-binding groove of the MHC type 2 molecule on the APC (see **Fig. 1**; **Fig. 5**). Many SAGs are believed to interact with selected TCR V β regions, and identification of this characteristic V β pattern or signature may be diagnostically useful. SAGs are capable of stimulating more than 20% of host T cells, more than that caused by conventional antigen presentation, and with intense potency.

There is also evidence for the direct action of SAGs at the tissue site. Norrby-Teglund and colleagues⁴⁴ examined tissue from patients with various GAS deep tissue infections, including NF and cellulitis. These investigators showed that the bacterial load and the magnitude and type of cytokine expression correlate with severity of GAS tissue infection. Detection of streptococcal SAGs in these tissue biopsy specimens, together with a typical SAGs cytokine response, provided strong support for the direct action of SAGs at the tissue site.

Superagonistic anti-CD28 antibodies

To mimic physiologic T-cell activation in vitro, monoclonal antibodies (mAbs) with specificity for the TCR complex and CD28 have proved useful. Neither anti-TCR mAbs alone nor conventional anti-CD28 mAbs by themselves suffice to fully stimulate T cells, whereas a combination of both efficiently induces T-cell proliferation and cytokine secretion. There is a subclass of CD28-specific antibodies, the CD28 superagonists, which are capable of fully activating T cells without additional stimulation of the TCR.⁴⁵ A CD28-specific mAb, TGN1412, was injected into 6 volunteers, as part of a phase 1 clinical trial.⁴⁶ All 6 recipients of the mAb suffered life-threatening severe adverse events, secondary to a cytokine storm, and required weeks of hospitalization, strongly resembling TSS.

M proteins

The inflammatory response to tissue injury or infection is characterized by changes in the microcirculation leading to impaired endothelial barrier function, plasma protein and fluid efflux, and extravasation of white blood cells. These adjustments are critical in the normal host defense, yet key elements in the pathogenesis of inflammatory

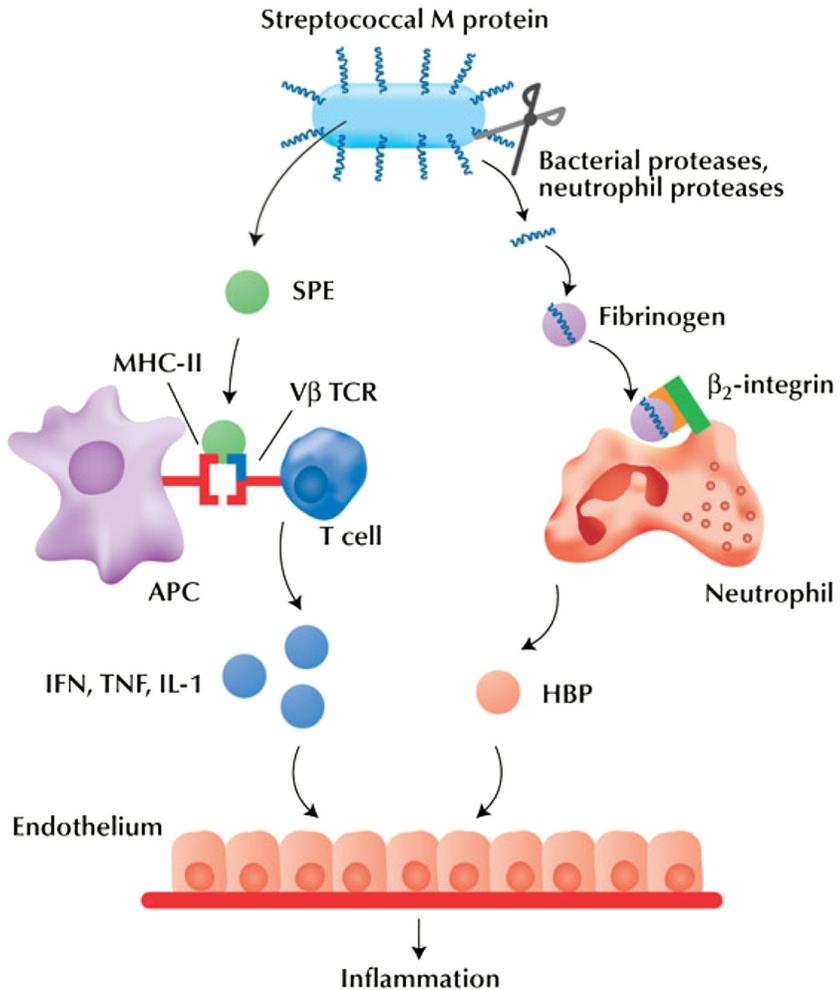


Fig. 5. Bacterial M protein induces shock. M protein is released from the streptococcal surface by neutrophil proteases and bacterial-derived cysteine proteases. M protein binds to fibrinogen, and these complexes subsequently bind to β_2 -integrins, adhesion molecules on the neutrophil surface. This binding results in neutrophil activation and the release of HBP, a potent inflammatory mediator. *Streptococcus pyogenes* also releases potent pyrogenic exotoxins (SPE), superantigenic toxins that can cross-link MHC class II molecules on APCs and the V β domains of T-lymphocyte receptors on T cells (T). This situation results in T-cell activation and the release of proinflammatory monokines. (From Cohen J. Shock factor shed by microbe. *Nat Med* 2004;10:342; with permission.)

disease. Vascular permeability is modified by inflammatory mediators acting directly on the endothelial cells, and by leukocytes stimulated by chemotactic factors. Polymorphonuclear leukocytes (PMNs), predominantly neutrophilic granulocytes, are the first white blood cells recruited to the inflamed tissue area. The alteration in vascular permeability evoked by chemotactic inflammatory mediators requires the presence of PMNs, or more specifically, an intact adhesive function of these cells. Leukocytic β_2 -integrins are critical in this respect, because inhibition of their receptor function

effectively prevents both PMN adhesion to the endothelial cell lining and the associated plasma leakage (see **Figs. 4** and **5**). The GAS M protein, in addition to its central role in the ability of the organism to colonize, evades phagocytosis by interfering with the complement pathway in a variety of ways, including binding factor H, and invades sterile sites. M protein plays a major role in activating neutrophils. M protein is released from the surface by the action of a cysteine proteinase, secreted by the bacteria, allowing it to bind fibrinogen, a constituent of blood plasma, with high affinity. The M protein-fibrinogen activates neutrophils by binding to β_2 -integrins, a family of adhesion molecules on the surface of neutrophils (see **Fig. 5**).⁴⁷ Binding of these integrins leads to the generation of toxic oxygen metabolites and the secretion of a variety of proteolytic and glycolytic enzymes, including HBP and resistin.

HBP

HBP (also known as azurocidin) is a multifunctional inflammatory mediator with the ability to induce vascular leakage.⁴⁸ The protein is contained within the secretory and azurophilic granulae of human neutrophils and is secreted on stimulation of the leukocytic membrane-bound β_2 -integrins. Linder and colleagues⁴⁹ in a prospective study of critically ill patients found that plasma HBP levels were significantly higher in patients with severe sepsis or septic shock compared with patients with nonseptic illness.

Resistin

Resistin belongs to a family of cysteine-rich peptides called resistinlike molecules, discovered in 2001 as an adipocyte-derived hormone that contributes to obesity-associated insulin resistance in mice. In humans, resistin has emerged as a potent proinflammatory molecule associated with acute and chronic inflammatory conditions, and levels of systemic resistin strongly correlate with the severity of sepsis. Johansson and colleagues⁵⁰ reported high levels of resistin in the circulation as well as at the local site of infection. Analyses of patient tissue biopsies and whole blood revealed that neutrophils represent a novel and dominant source of resistin in bacterial septic shock. These analyses found that resistin release was readily triggered by the streptococcal M1 protein.

STSS and lung injury

The lung damage observed in STSS has been postulated to be caused by several virulence mechanisms, including activation of monocytes, T cells and platelets, as well as the secretion of chemokines, cytokines, and tissue factor.⁵¹ However, Soehnlein and colleagues⁵¹ found in a mouse model evidence of an almost exclusive role of the intravascular activation of PMNs and the subsequent discharge of granule proteins in the onset of the M1 protein-induced lung edema and lung damage. Intravenous injection of M1 protein into mice induced neutrophil accumulation in the lung, increase in vascular permeability, and acute lung damage. Depletion of neutrophils from the circulation completely abrogated lung injury and vascular leakage. These investigators also found that the M1 protein-fibrinogen complexes activate PMNs intravascularly, so that a direct interaction between PMNs and the endothelium is not necessary for the development of the lung injury.

GAS NF

Although NF is a separate disease entity, concomitant TSS occurs in approximately 50% of patients with NF.³² Like TSS, NF is principally a toxin-mediated disease. Once the strain of GAS has infected the soft tissue, toxins are released, which start a cascade of events that are now independent of the presence of the organism.

Many host-derived mediators are released from plasma proteins (the coagulation, fibrinolytic, and complement systems) or cells (endothelial cells, monocyte macrophages, and neutrophils). These endogenous mediators have a profound physiologic effect on vasculature and multiorgan systems. Not only is the virulence potential of any GAS strain determined by its repertoire of virulence factor genes but it is also significantly influenced by transcriptional regulators. The sensor kinase (CovS) component or the transcriptional repressor (CovR) component of the CovR/CovS 2-component regulatory system CovR/CovS responds to a variety of environmental cues that may signal the transposition of a GAS organism from a mucosal to an invasive site. Coagulopathy, a well-recognized clinical feature of GAS NF, is a result of the dysregulation of the delicate balance between host procoagulant and thrombolytic activity. Streptococcal cysteine protease B, a protease with numerous substrates, including many physiologically important human proteins, as well as its own virulence factors, is highly expressed at the tissue site of infection in patients with NF.^{38,52} Similar to the link between proinflammatory cytokine responses in circulation and the severity of invasive streptococcal infections,^{26,53} a significant correlation exists between *in vivo* inflammatory responses at the infected tissue site and the severity of streptococcal tissue infection.⁴⁴ Infiltration of PMNs in superficial fascia and dermis is one of the histopathologic criteria for diagnosis of NF. This finding was also evident in the patient tissue material, in which neutrophils represented one of the dominant cell populations and the degree of infiltration correlated significantly with bacterial load.³⁸ Soluble M1 protein and M1 protein/fibrinogen complexes have been shown in patient biopsy specimens, which underlines the potential pathophysiologic significance of these complexes generated during infection.⁴⁷ This finding is further substantiated by the presence of neutrophil proteins at the infected tissue site, including HBP, interleukin 8 (IL-8), resistin, and LL-37, all of which are likely to contribute to the hyperinflammatory state that characterizes these infections.⁴⁸

MANAGEMENT

Staphylococcal TSS

Treatment of TSS includes appropriate use of antibiotics, identifying the source of the infection, drainage of wounds (including removal of the tampon in menstruation-associated staphylococcal TSS) and supportive care. Anecdotal evidence also suggests that treatment with intravenous immunoglobulin (IVIG) decreases the likelihood of mortality in cases of staphylococcal TSS, presumably by neutralizing the activity of the SAg toxins.

STSS

Antimicrobials

Penicillin is the first-line antibacterial of choice for invasive GAS disease. Clindamycin is a useful and important adjunctive antibacterial in cases of STSS and severe GAS infection, especially necrotizing fasciitis. Clindamycin inhibits protein synthesis by acting at the 50S ribosome. Although there is some laboratory evidence that clindamycin has advantages over β -lactam antibacterials in severe gram-positive infections, there is only limited clinical evidence in retrospective studies to support its use.⁵⁴ Clindamycin should be used as an additive antibacterial, not as a replacement for penicillin.

IVIG

The finding that lack of protective antibodies against streptococcal M protein and SAGs correlated with risk of developing invasive streptococcal diseases⁵⁵ highlighted the importance of antibodies in protection against these infections and suggested that

Mechanism of antiinflammatory effect of IVIG

- Decreases in the production of proinflammatory cytokines
 - Tumor necrosis factor α
 - IL-1 α and IL-6
- Downregulation of adhesion molecule and chemokine and chemokine-receptor expression
- Neutralization of SAGs

IVIG might be a potential adjunctive therapy. IVIG shows high polyspecificity generated by antibodies pooled from several thousands of donors and has been shown to contain broad-spectrum antibodies against streptococcal SAGs and M proteins.^{56–59} In addition, IVIG has a general antiinflammatory effect, which is attributable, in large part, to Fc-receptor mediated mechanisms. The documentation of clinical efficacy of IVIG in STSS includes several case reports, as well as 2 observational cohort studies, 1 case control study, and 1 multicenter placebo-controlled trial. The case control study was designed to evaluate the efficacy of IVIG therapy in patients with STSS and included 21 patients who were treated with IVIG during 1994 to 1995 and 32 nontreated control individuals identified through active surveillance of invasive GAS infections during 1992 to 1995.⁶⁰ Multivariate analysis revealed that IVIG therapy and a lower APACHE (Acute Physiology and Chronic Health Evaluation) II score was significantly associated with survival. To further document the safety and efficacy of this adjunctive therapy, a multicenter placebo-controlled trial of IVIG in STSS was initiated in Europe.⁶¹ The trial was prematurely terminated because of a low incidence of disease in the participating countries and, consequently, a slow patient recruitment. Results were obtained from 21 enrolled patients (10 IVIG recipients and 11 placebo recipients). The primary end point was mortality at 28 days, and a 3.6-fold higher mortality was found in the placebo group. This trend to improved survival was strengthened by the significant improvement in organ function revealed by the reduction in the sepsis-related organ failure assessment score after treatment, which was evident in the IVIG group but not in the placebo group. Furthermore, a significant increase in plasma-neutralizing activity against SAGs expressed by autologous isolates was noted in the IVIG group after treatment. In an observational case study involving patients with severe GAS soft tissue infections,⁶² the use of an aggressive medical regimen, which included high-dose IVIG together with a conservative surgical approach, was studied. The report describes 7 patients with severe soft tissue infection caused by GAS who did not undergo surgery or for whom only limited exploration was performed. Six of the patients had STSS, and they all received effective antimicrobial therapy and high-dose IVIG. All patients survived. Tissue biopsy specimens collected from the same surgical site at different time points after IVIG administration was available from 1 patient. Analyses of bacterial load, SAg, and inflammatory cytokines in the biopsy specimens revealed dramatic improvement in all markers at the later time point (**Fig. 6**). This observational study, although limited in numbers, suggests that an initial conservative surgical approach combined with the use of immune modulators, such as IVIG, may reduce the morbidity associated with extensive surgical exploration in hemodynamically unstable patients without increasing mortality.

Surgery: is it time to reconsider the dogma?

The dogma for the management GAS NF is that once NF is suspected, early surgical debridement is warranted (**Table 2**). It is curious, that despite the lack of clinical or

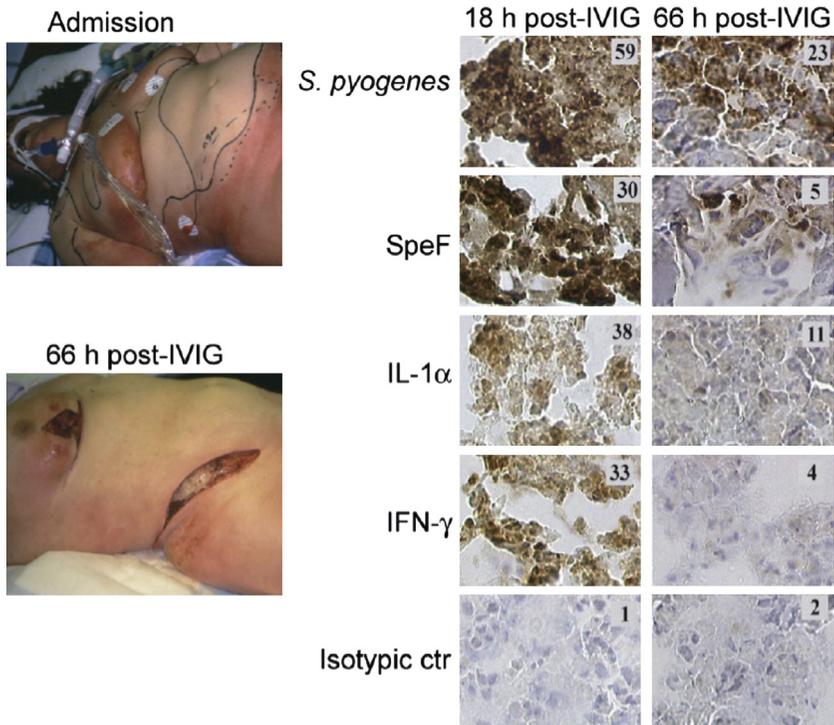


Fig. 6. Bacterial factors and inflammatory responses in same site tissue biopsy specimens after administration of IVIG, showing the extent of tissue infection at hospital admission and after 66 hours in a patient with NF. Tissue biopsy specimens taken from the same surgical site at 18 and 66 hours, respectively, after IVIG therapy were immunostained for specific factors, as indicated in the figure. The stains were quantified by acquired computed image analysis, and image analysis data are indicated in each image. ctr, control; IFN, interferon; *S. pyogenes*, *Streptococcus pyogenes*. (From Norrby-Teglund A, Muller MP, McGeer A, et al. Successful management of severe group A streptococcal soft tissue infections using an aggressive medical regimen including intravenous polyspecific immunoglobulin together with a conservative surgical approach. *Scand J Infect Dis* 2005;37:169; with permission.)

scientific evidence to support this statement, it is widely endorsed in standard textbooks of surgery,⁶³ infectious disease,⁶⁴ and internal medicine,⁶⁵ and treatment guidelines from infectious disease, critical care, and surgical societies,^{42,66,67} as well as review articles.^{21,68} The published studies cited are all based on retrospective chart review of patients with NF with multiple causes, including mixed aerobic and anaerobic organisms (see **Table 2**). Only the study by Schurr and colleagues⁶⁹ consisted of all GAS NF cases. In this study, delay to surgical referral was 5 ± 3 days. Patients were managed with single debridement before grafting. None of the 14 patients died.

What is the rationale for immediate extensive tissue debridement in patients with GAS NF?

1. To manage sepsis. There seems to be a belief that removing the infected necrotic tissue controls or minimizes the effect of sepsis. However, there is overwhelming evidence that in patients with STSS, SAGs induce a systemic inflammatory

Table 2

A review of 19 retrospective studies on the management of patients with NF

Reference	Number of Centers	Time Period Cases Accrued	Number of Patients with NF ^a	Wound Culture Results				Mortality (%)	Comment	Surgery	Investigators' Comment
				No. Pos.	No. Mixed	GAS					
						Mono	Mixed				
⁷⁴	1	1954–1969	44	43	INP	5	14	30		TA/DS: 4 d in survival group	“The most important factor in survival was related to rapidity of diagnosis and institution of therapy”
⁷⁵	Group A	1	1965–1980	20	20	20 mixed	β-streptococcus	50	No treatment protocol	TA/DS not stated	“Survival directly related to aggressive surgical debridement at the time of diagnosis”
	Group B	Multiple	1980 to 1982	10	10	10 mixed	one of most commonly isolated organisms	0	Treated according to protocol		
⁷⁶	2	1958–1982	21	13	4	1	0	52		TA/DS <24 h 70% survival vs 36% >24 h	“Radical operative debridement should be performed immediately after resuscitation”

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Table 2
(continued)

Reference	Number of Centers	Time Period Accrued	Number of Patients with NF ^a	Wound Culture Results				Mortality (%)	Comment	Surgery	Investigators' Comment
				No. Pos.	No. Mixed	GAS					
						Mono	Mixed				
⁷⁷	1	1979–1988	14	14	14	0	1	43		In 7 patients were surgery <4 d from admission survived	"Delayed diagnosis and inadequate surgery are the most important factors contributing to the mortality"
⁷⁸	1	1980–1988	18	18	16	2	5	33		3 of 4 patients died as a result of a delay in surgical debridement for more than 24 h after admission	"Early diagnosis and prompt surgical debridement for NF are essential for survival"
⁷⁹	1	12-y period	42	27	27	0	6 <i>Streptococcus</i> spp	26		Mortality 7% in those who underwent radical surgical in the first 24 h	"Early radical surgical treatment is confirmed as the most important factor affecting outcome"

80		1	1989–1994	65	64	45	10	2	29		The average time from TA/DS was 90 h in nonsurvivors vs 25 h in survivors	“Early debridement was associated with a significant decrease in mortality”
81		1	1985–1993	198	182	154	15	68	25.3	All patients but 6 from elsewhere	Survivors TA/DS 1.2 d vs 3.1 d for nonsurvivors	“Best treated with early and repeated extensive debridement”
82		1	15 y, dates not given	12	12	12	β- <i>Streptococcus</i> one of most commonly isolated organisms		0		Data not available	“Early diagnosis and aggressive surgical debridement”
83	Group A	1	1980–1996	21	3	3	0	0	38		Delay in treatment or limited debridement	“Early recognition and prompt wide surgical debridement at time of presentation”
	Group B	1		47	11	7	1	1	4.2		Wide surgical debridement	
69		1	1989–1995	14	7	7	7	7	0	5 patients met criteria for STSS	Delay in initially seeking medical care and surgery was 5 ± 3 d	“Single radical debridement with preservation of fascia maximizes limb salvage and survival”

(continued on next page)

Table 2
(continued)

Reference	Number of Centers	Time Period Cases Accrued	Number of Patients with NF ^a	Wound Culture Results				Mortality (%)	Comment	Surgery	Investigators' Comment	
				No. Pos.	No. Mixed	GAS						
						Mono	Mixed					
84	1	1997–2002	89	73	48	8 patients had GAS alone or in combination with <i>Staphylococcus aureus</i>		21.3		A delay in TA/DS >24 h was correlated with increased mortality	"Early operative debridement was demonstrated to reduce mortality"	
85	1	2003–2005	52	35	19	INP		9.6		Median time TA/DS was 8.6 h. Shorter time TA/DS was associated with better survival	"More rapid diagnosis and debridement is likely to enhance survival"	
86	1	2002–2005	128	99	30	8 patients had GAS alone or in mixed culture of wound		19	High proportion of <i>Vibrio</i> and <i>Aeromonas</i> spp	Early operative procedures were not a predictor of mortality	" <i>Vibrio</i> and <i>Aeromonas</i> spp had higher mortality"	
87	Only ICU patients	1	1996–2004	106	44	38	1	26	40.6	Time from A/DTS assessed in 54 patients	TA/DS >14 h compared with ≤14 h in patients with septic shock	"Hospital mortality is influenced by the timing of surgical treatment"

88	TA/DS ≤12 h	1	2004–2010	22	21	13	7 patients had GAS alone or in mixed culture from wound	4.5		Mortality was significantly lower in patients who underwent early surgical debridement	"Delay in treatment beyond 12 h is associated with a significant increase in the number of debridements required"
	TA/DS >12 h	1	2004–2010	25	25	16	8 patients had GAS alone or in mixed culture from wound	28			
89		6	2004–2007	296	239	110	14		17	TA/DS >24 h was not significantly associated with mortality	"Patients should be treated promptly and aggressively"
89	Only ICU patients	1	2000–2011	24	22	9	11 patients had GAS alone or in mixed culture from wound	8.3	Relatively healthy younger population (52.5 y)	The median time TA/DS 20 h, with 70% of patients TA/DTS 24 h	"Surgical debridement in less than 24 h"
90		1	2008–2011	54	34	11	6 patients with GAS cultured.	33 for TA/DS <12 h and 56 for those ≥12 h		Delayed TA/DS did not significantly affect mortality	"Surgical delays did not impact mortality"

Abbreviations: INP, information not provided; TA/DS, time from admission/diagnosis to surgery.

^a Diagnosis made either by histologic findings or clinical findings at surgery.

response, which results in shock.^{43,44,70,71} Even a short burst of SAGs can have systemic effects that last for more than 8 days.⁴⁶ Delaying surgery may decrease morbidity by allowing the development of a line of demarcation separating necrotic from vital tissue, thereby limiting the extent of tissue resection. It may also decrease mortality by allowing the patient to stabilize hemodynamically before surgery.

2. The need to remove necrotic infected tissue. The necrotic tissue is thrombosed and therefore avascular. Early versus late surgical debridement has been a matter of debate also in acute necrotizing pancreatitis, in which a common therapeutic approach in the past was early surgical intervention and debridement. However, Mier and colleagues⁷² found that early surgical intervention in severe necrotizing pancreatitis was deleterious, resulting in mortality exceeding 50%, whereas delayed surgical debridement along with close supportive care improved the clinical outcome. A consensus conference on the management of necrotizing pancreatitis recommended that intervention was primarily indicated for infected necrosis, less often for symptomatic sterile necrosis, and should ideally be delayed as long as possible, preferably 4 weeks or longer after the onset of disease, for better demarcation and liquefaction of the necrosis.⁷³
3. To stop the spread of infection. Concern is often raised in the literature that removal of necrotic and surrounding tissue is required to prevent the spread of infection. However, patients presenting with NF are often bacteremic and the organism has had the opportunity to spread to distal sites. Bacteremia was found in 1 report in 88% of cases.³¹ Thulin and colleagues,³⁸ who analyzed snap-frozen tissue biopsy specimens collected from patients with NF or severe cellulitis, detected bacteria in all biopsy specimens, even those collected from distal areas. Biopsy specimens obtained as late as 20 days after diagnosis of infection and initiation of intravenous antibiotics still contained bacteria.³⁸ Although GAS NF is often a fulminant bacteremic infection, delay in diagnosis of several days is not uncommon.³⁴ Therefore it is difficult to imagine that the infection has not had the opportunity to spread to more distal tissues and that physical removal of tissue prevents this.
4. The need to do something. These patients are very ill, with dramatic presentations. When standard textbooks recommend immediate surgery, it is difficult to object. At the time of admission of the patient depicted in **Fig. 6**, she had STSS and NF and it was believed that she would need a 70% debridement of her skin and soft tissue. However, because she was unstable, we were able to convince the surgical team to wait 24 hours, at which time there was evidence of clinical improvement. She continued to improve. She underwent surgical exploration and biopsies at only the 2 sites noted in the photograph.

In patients with STSS, the mortality is approximately 50%,⁵ whereas in patients with NF without STSS, the mortality is 5%.³² Delaying surgery may decrease morbidity by allowing the development of a line of demarcation separating necrotic from vital tissue, thereby limiting the extent of tissue resection. It may also decrease mortality, by allowing the patient to stabilize hemodynamically before surgery. However, any necrotic tissue should eventually be removed, but if the use of an immunomodulating agent, such as IVIG, which neutralizes the toxins and the pathologic levels of proinflammatory cytokines, allows for the tissue debridement to be performed at a later stage, this may be beneficial for the patient.

SUMMARY

Staphylococcal TSS and STSS, although uncommon, are associated with significant morbidity and mortality. TSS is primarily the result of a SAG-mediated cytokine storm

and M protein-mediated neutrophil activation, resulting in the release of mediators, leading to respiratory failure, vascular leakage, and shock. Advances in medical care and the use of cell wall-inhibiting and protein-inhibiting antimicrobials have not reduced the morbidity and mortality caused by TSS. IVIG, with its broad-spectrum antibodies against SAGs and streptococcal M proteins and its general antiinflammatory effect, seems to be a promising adjunctive therapy. The use of IVIG in patients with streptococcal NF may allow a more conservative surgical approach during the acute phase of the illness, thereby reducing the risk of extensive tissue debridement in the acutely ill patient.

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