REVIEW ARTICLE

Drugs 2012; 72 (9): 1213-1227
0012-6667/12/0009-1213/$55.55/0

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Invasive Group A Streptococcal Disease
Epidemiology, Pathogenesis and Management

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Contents

Abstract

Invasive group A streptococcal infections are uncommon, although serious, infections with high case fatality rates. Periodic resurgences in invasive group A streptococcal infections in industrialized countries have been reported from the 1980s onwards, with current estimates of incidence in these countries of approximately 3–4 per 100 000 population. Infants, pregnant women and the elderly are at increased risk of invasive group A streptococcal infection. The group A streptococcus has an array of virulence factors that underpin its invasive capacity and, in approximately 10% of cases, superantigen toxins produced by the bacteria stimulate a large proportion of T cells, leading to streptococcal toxic shock syndrome. Given the rapid clinical progression, effective management of invasive group A streptococcal

infections hinges on early recognition of the disease and prompt initiation of supportive care (often intensive care) together with antibacterial therapy. In cases of toxic shock syndrome, it is often difficult to distinguish between streptococcal and staphylococcal infection before cultures become available and so antibacterial choice must include coverage of both of these organisms. In addition, clindamycin is an important adjunctive antibacterial because of its anti-toxin effects and excellent tissue penetration. Early institution of intravenous immunoglobulin therapy should be considered in cases of toxic shock syndrome and severe invasive infection, including necrotizing fasciitis. Early surgical debridement of necrotic tissue is also an important part of management in cases of necrotizing fasciitis.

The group A streptococcus (GAS) is a Gram-positive bacterium that causes a wide diversity of clinical disease in humans, ranging from pharyngitis and impetigo, to post-streptococcal immunological sequelae, such as acute rheumatic fever and acute glomerulonephritis, to invasive infections. The definition of an invasive infection is one in which GAS infects a normally sterile site. These infections are serious, with a high case fatality rate, especially when associated with streptococcal toxic shock syndrome (STSS).[1,2] Invasive GAS infections are life-threatening infections that require early recognition, aggressive treatment and specific therapies for successful management.

1. Epidemiology

The epidemiology of GAS diseases has changed dramatically over the course of the past few centuries. Historical literature describes epidemics of scarlet fever in many European countries during the 19th and early 20th centuries, which – unlike cases identified in modern times – presented with fulminant sepsis and high risk of mortality. It is likely that many of these severe cases of scarlet fever described in the earlier part of the 20th century would meet modern-day clinical definitions of invasive GAS infection with STSS.[3,4] However, STSS was first formally described in 1984 in a 37–year-old woman in Prague,[5] with further reports in adults[6,7] and children[8-10] when STSS became established as a disease entity. Scarlet fever became less common in the industrialized world during the middle part of the 20th century for reasons that are not fully understood (figure 1). Improvements in living conditions, nutrition and application of strict control measures are likely to have played a role in driving down rates of disease, although the pathogenicity of circulating GAS strains also may have altered over time. Given that the decrease preceded the availability of antibacterials, this suggests a lesser role for improvements in therapy in driving down incidence of disease.

Periodic upsurges in the incidence of invasive GAS infections began to be reported in Europe and Australia during the 1980s and persist to this day.[12-17] A compilation of the incidence rates of invasive GAS disease shows remarkable consistency between industrialized nations, with rates largely between 2 and 4 per 100 000 (table I). As a comparison, this is two to four times higher than the incidence of meningococcal disease in the US.[31] Incidence of invasive GAS infection is typically higher in winter and spring and lowest in autumn.[20,24,32-36]

Anecdotal reports and limited published data suggest that the rates of invasive GAS disease are several-fold higher in developing countries (over 10 per 100 000) in keeping with the observation of a high burden of other GAS diseases in these areas, including GAS impetigo, post-streptococcal glomerulonephritis and acute rheumatic fever (table I).[37] A review of global data in 2005 estimated that 97% of the 663 000 cases and 163 000 deaths due to invasive GAS disease per year occur in developing countries.[37] However, these figures almost certainly underestimate the true disease burden in developing countries because of

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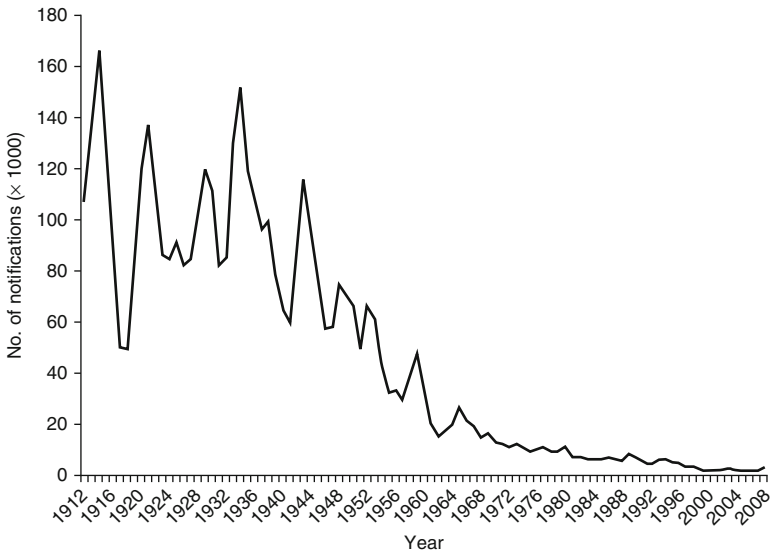

Fig. 1. Notifications of scarlet fever in England and Wales, 1912–2007.[11]

a lack of high-quality surveillance data from most tropical developing countries.

Morbidity and mortality from invasive GAS disease is significant. Estimates of case fatality have varied between studies, but mean case fatality rates in affluent countries range from 8% to 16%.[2,14,38] This rate is similar to, if not higher than, that of invasive meningococcal disease.[31] One in five patients with invasive GAS disease will be admitted to an intensive care facility and one in four will undergo surgery.[39] Case fatality rates in middle- and lower-income countries are even higher, with reported rates above 25%.[27,28,40] Case fatality rates in both affluent and resource-poor countries approach 50% in the presence of STSS.[30]

1.1 Factors Predisposing to Invasive Group A Streptococcal Infection

A number of common factors have been identified as predisposing to invasive GAS infection, although not all have been robustly tested in epidemiological studies. Studies in varied locations have found higher rates of disease at the extremes of age (figure 2), and in males compared with females, although infection can occur at any age in otherwise healthy individuals.[2,32,33,39] Differences in rates of infection by ethnic group have also been identified in a number of studies, with individuals of White European descent typically having lower rates of disease than non-Whites.[2,30,41]

Skin lesions, either traumatic, surgical or due to chronic skin conditions are the most common risk factors identified, although most patients do not have an identifiable focus of infection.[1,2,23,42] A number of pre-existing medical conditions have been associated with increased risk of infection, including heart disease, diabetes and malignancy.[1,2,14,20,23,42-45] Influenza is also known to predispose to invasive GAS infection, with a substantial number of deaths during the Spanish influenza pandemic of 1918 attributed to GAS infection.[46] More recent evidence during the H1N1 virus pandemic points to a substantial impact of influenza on predisposition to invasive GAS infection.[17,47] Injecting drug users have also been found to be at increased risk of invasive GAS infection, probably due to the direct risk of injecting in creating a portal of entry and indirectly due to poor living conditions and additional comorbidities.[48-50]

Varicella infection is an important predisposing factor in children, particularly for soft tissue infection, including necrotizing fasciitis.[19,51-56]

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The mechanism by which varicella predisposes to necrotizing fasciitis is not clear.[55] It may be that pox lesions act as a portal of entry to the dermal and fascial layers, or that varicella infection itself causes immunosuppression, particularly a decrease in humoral immunity.[19] The latter explanation is supported by the fact that patients tend not to have secondarily infected pox lesions overlying the area of necrotizing fasciitis,[54] and because STSS and invasive GAS disease without necrotizing fasciitis may also follow varicella infection.[57-59] The median duration of varicella vesicles before developing symptoms of necrotizing fasciitis is 3–4 days.[53,54]

Whilst cases of invasive GAS infection associated with pregnancy and childbirth are rare in industrialized countries, representing 2–4% of all invasive cases, the postpartum period confers a substantial elevation in risk for a range of clinical manifestations.[39,60,61] Of the estimated 8–12% of all maternal deaths in developing countries due to maternal sepsis, a significant proportion is likely to be due to GAS.[62] Whilst maternal deaths due to sepsis in industrialized countries are considerably less common than in resource-poor settings,[62] a worrying increase in genital tract sepsis deaths was noted recently in the UK, now the most common cause of maternal death. Of the genital tract sepsis deaths with an organism identified, the majority were attributed to GAS.[63] A number of studies have also documented an onward risk of invasive disease in the neonates born to mothers who developed GAS infection.[64-66]

2. Pathogenesis and Microbiology

The GAS is a highly pathogenic organism with a multitude of virulence factors that are both cell-surface attached and secreted.[67] The major virulence factor of the GAS is the M protein, which

Table I. Population-based surveys of invasive group A streptococcal disease and streptococcal toxic shock syndrome

Location (state), year of study	Age	Incidence of invasive GAS disease (per 100 000)	Case fatality ratio of invasive GAS disease (%)	Reference
Industrialized nations				
Australia (QLD), 1996–2001	All	10.2	7	18
Australia (VIC), 2002–4	All	2.7	8	14
Canada (ON), 1992–6	All	1.9	10	19
Canada (AB), 2000–2	All	3.8	11	20
Denmark, 1981–93	All	1.6	23	21
Denmark, 2003–4	All	2.58	16	1
Finland, 2007	All	3.90	NA	22
Israel, 1997–8	All	3.7	5–14	23
Netherlands, 2002	All	3.10	NA	24
Sweden, 1993–6	All	2.9	16	25
Sweden, 1996–7	All	2.3	11	26
Sweden, 2003–4	All	3.10	9	1
UK, 2003–4	All	3.31	19	1
USA (ten states), 2000–4	All	3.5	14	2
Developing countries (and disadvantaged communities in industrialized countries)				
Australia (indigenous Australians), 1996–2001	All	82.5	7	18
Fiji, 2000–5	All 0–5 y	11.6 26	29	27
Kenya, 1998–2002	0–15 y 0–1 y	13 96	25	28
New Caledonia, 2006	All	38	3	29
USA (AZ – Native American), 1985–90	All	46	20	30

AB = Alberta; **AZ** = Arizona; **GAS** = group A streptococcus; **NA** = information not available; **ON** = Ontario; **QLD** = Queensland; **VIC** = Victoria.

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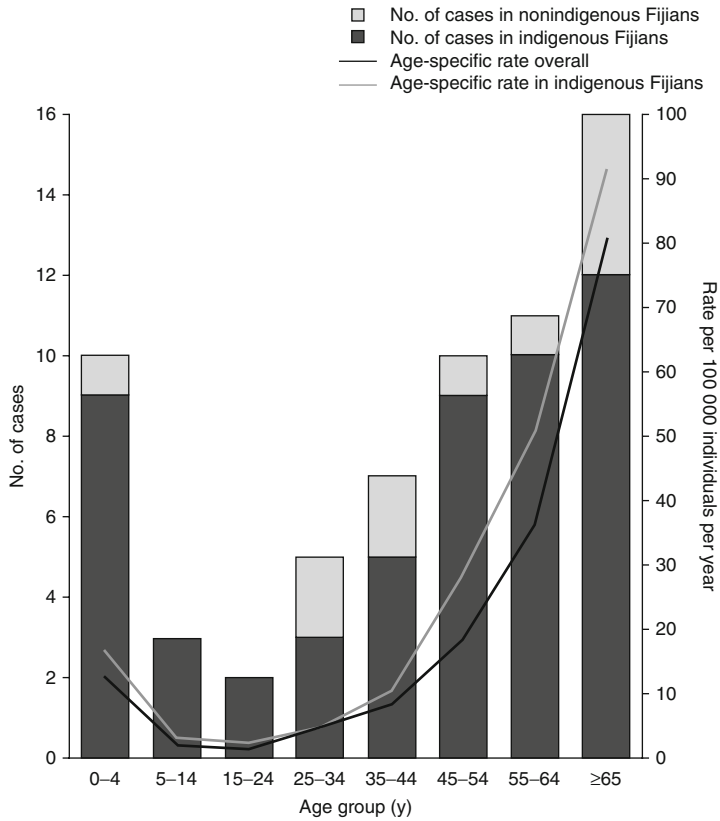

Fig. 2. The age-distribution of invasive group A streptococcal disease in Fiji (reproduced with permission from Steer et al.[40]).

plays a central role in the organism's ability to colonize, evade phagocytosis and invade sterile sites.[68] The GAS is able to colonize mucosal surfaces by attaching to epithelial cells using bacterial cell surface proteins that act as adhesins, including M and M-like protein, lipoteichoic acid and the fibronectin-binding proteins.[69,70] Invasion beyond the epithelium is aided by secreted tissue-degrading enzymes such as streptokinase, the DNases and hyaluronidase.[67] The GAS is able to evade the initial immune response by a number of mechanisms. The M protein resists phagocytosis by neutrophils by interfering with the complement pathway in a variety of ways including binding Factor H.[71] The hyaluronic acid capsule also plays an important role in resisting phagocytosis and the enzyme C5a peptidase limits recruitment of phagocytes.[72,73]

Like *Staphylococcus aureus,* the GAS is able to produce exotoxins that act as superantigens. These superantigens are responsible for the clinical features and high case fatality rate of STSS. The best characterized of these exotoxins is streptococcal pyrogenic exotoxin A, although multiple other streptococcal superantigens have been identified.[74] Superantigens are immunomodulatory proteins that stimulate T cells by directly binding Class II molecules on antigen-presenting cells (e.g. dendritic cells, B cells and macrophages) to the T-cell receptor. Superantigens bypass the antigen processing and major histocompatibility complex (MHC) restriction that is necessary for conventional antigens presented in the binding groove of the MHC II molecule.[74-79] This less specific interaction leads to the stimulation of a large proportion (up to 20%) of all circulating

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T cells and a consequent release of pro-inflammatory cytokines from T cells and other cells of the immune system.[78] This intense inflammatory cascade is responsible for the clinical features of STSS.[80]

Differentiating between strains of GAS is conventionally done by *emm* typing, which refers to sequence typing of the hypervariable region of the M protein gene.[81] There are over 200 known *emm* types of GAS.[82] In industrialized countries in temperate zones, 25 *emm* types account for nearly 95% of disease, with four types (*emm1, emm28, emm3, emm12*) accounting for 50% and *emm* type 1 alone accounting for 23% of disease.[82] Longitudinal analyses show marked variations in *emm* type distributions over time, with sudden increases in overall disease incidence often accompanied by increases in *emm*1 or *emm*3.[35,83,84] Although there are no definitive data, the repertoire and proportions of *emm* types causing invasive disease in these countries are probably similar to those that cause pharyngeal infection.[82] The explanation for why invasive disease occurs in some people and not others when they are exposed to GAS is not clear. Circulating *emm* types may acquire virulence factors that permit them to invade into sterile sites,[85,86] but host and environment factors also play an important role in susceptibility. In tropical developing countries there is a wide variety of *emm* types that cause invasive disease without dominant *emm* types such as *emm*1.[27,82,87] For example, in the Pacific region, 19 *emm* types account for 50% of invasive disease and *emm*1 accounts for less than 4%.[82]

3. Clinical Features

The GAS is able to invade a wide variety of sterile sites. The soft tissues are the most common site of invasive GAS infection (up to 50% of cases). Necrotizing fasciitis is a rare but particularly severe form of soft tissue invasive GAS disease and is often associated with STSS.[44] Bacteraemia without an identified focus occurs in approximately 15% of cases of invasive GAS disease. Other clinical syndromes caused by invasion of GAS into sterile sites include pneumonia, osteomyelitis, septic arthritis and meningitis.

3.1 Necrotizing Fasciitis

Necrotizing fasciitis is a severe and rapidly spreading infection of muscle fascia, subcutaneous fat and epidermis that leads to necrosis of muscle fascia.[88] Necrotizing fasciitis can be polymicrobial caused by mixed anaerobic and Gram-negative bacteria (so-called Type I necrotizing fasciitis) or it can be caused by GAS (Type II).[89] The highly tissue destructive nature of GAS-associated necrotizing fasciitis has earned GAS the reputation of the 'flesh-eating bacterium' in the popular press. Necrotizing fasciitis may follow local blunt or penetrating trauma to the skin. It occurs most commonly in the upper limb, followed by the lower limb. In adults, necrotizing fasciitis can be associated with intravenous drug use, whilst in children, varicella is a common precipitant.[90,91] Patients with GAS-associated necrotizing fasciitis may only have subtle signs of severity at initial presentation and can therefore be difficult to differentiate from a relatively simple cellulitis. Severe pain and tenderness that is disproportionate to the physical findings is the clinical hallmark that differentiates necrotizing fasciitis from more superficial infection.[88,92] Tense oedema and the development of bullae that appear bluish as the disease progresses are also useful signs, but are often late signs and indicative of significant tissue necrosis.[93,94] The case fatality rate of GAS-associated necrotizing fasciitis is 30–50%,[88,90,91,93] and the majority of deaths occur in the first 48 hours after presentation, reflecting the rapidly progressive nature of the disease.[19] Between 30% and 50% of patients with GAS-associated necrotizing fasciitis develop STSS and these patients have a particularly high case fatality rate.[54,88,91]

3.2 Streptococcal Toxic Shock Syndrome

STSS is characterized by fever and rash, with rapid progression to shock and multi-organ failure. Fifty percent of patients have hypotension at presentation, and by 4 hours all develop hypotension.[95] The typical 'sunburn' type rash in STSS is widespread, erythematous, macular and

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blanching. Characteristically, there is subsequent desquamation about 2 weeks after the initial illness. In addition to fever and rash at presentation, there may be the presence of non-purulent conjunctivitis and mucositis. Shock is caused by the capillary leak and vasodilation resulting from the massive cytokine release induced by bacterial superantigen toxins, and, untreated, leads to hypotension, disseminated intravascular coagulation, myocardial suppression, renal failure and adult respiratory distress syndrome (ARDS). Thrombocytopenia and abnormal liver function are other manifestations of STSS. Streptococcal toxic shock has been described in association with all manner of invasive GAS infections, but soft tissue infection, in particular necrotizing fasciitis, is the most common associated focus of infection.[44,94]

4. Diagnosis

The diagnosis of invasive GAS disease is usually only made when culture results of fluid or tissue from a sterile site become available because there is usually little to distinguish GAS invasive disease from other bacterial causes of sepsis or focal invasive disease, particularly those caused by *S. aureus*. However, GAS infections are often more severe, more likely to cause complications and are often slower to respond to treatment; this is particularly true of GAS pleural empyema.[96] STSS is almost always associated with an invasive GAS infection, whereas the precipitating infection in staphylococcal toxic shock syndrome is often superficial or mucosal.

4.1 Diagnosis of Necrotizing Fasciitis

If the diagnosis of necrotizing fasciitis is not clear, there are a number of investigations available to the clinician. There are some reports of the usefulness of magnetic resonance imaging (MRI).[97-99] The use of frozen section biopsy specimens of suspected areas of tissue may enable early recognition of necrotizing fasciitis and institution of appropriate treatment.[100] However, if MRI is not available or if pathology staff are unable to interpret frozen section specimens, or whenever there is a strong suspicion of necrotizing fasciitis, then specific treatment should not be delayed.[101] A scoring system using haematological and biochemical results at admission has also been developed to aid the clinician in the early recognition of the disease.[102] However, the use of this and other similar scoring systems has not been widely validated.

4.2 Diagnosis of Streptococcal Toxic Shock Syndrome

The diagnosis of STSS is based upon criteria published in 1993 (table II).[103] These criteria were designed primarily for research purposes, with high specificity to identify established cases, and therefore have poor sensitivity to diagnose the syndrome early in their course. Before the onset of capillary leak sufficient to cause shock with resulting end-organ failure, patients may present with only fever and rash, sometimes with additional characteristic features such as conjunctivitis or mucositis. The absence of sufficient features to fulfil the formal diagnostic criteria should not deter early provisional diagnostic and empiric treatment of STSS.

Toxic shock syndrome can also be caused by *S. aureus*. Patients with staphylococcal toxic shock syndrome are more likely to have the macular

Table II. Diagnostic criteria for streptococcal toxic shock syndrome[103]

Streptococcal toxic shock syndrome – case definition
1. Isolation of GAS
A. From a sterile site (definite case)
B. From a non-sterile site (probable case)
2. Clinical signs of severity
A. Hypotension AND
B. Two or more of the following clinical and laboratory abnormalities:
a. Fever (>38.5°C)
b. Rash (diffuse macular erythema with subsequent desquamation)
c. Renal impairment
d. Coagulopathy (platelets <100 or DIC)
e. Liver function abnormalities
f. ARDS
g. Extensive tissue necrosis (including necrotizing fasciitis)

ARDS = adult respiratory distress syndrome; **DIC** = disseminated intravascular coagulation; **GAS** = group A streptococcus.

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erythematous rash that desquamates than patients with STSS, and patients with STSS are much more likely to have positive blood cultures (60–80% in STSS[30,36,44] compared with as few as 3% in staphylococcal toxic shock syndrome).[104] However, these observations are generally unhelpful early in the disease when treatment needs to be instigated.

5. Clinical Management

Because of the severe nature of many invasive GAS infections, aggressive supportive care and early targeted antibacterial therapy are the most important aspects of management, particularly of STSS. However, there are also a number of considerations unique to invasive GAS infection: removal of infected tissue, use of intravenous immunoglobulin (IVIG); use of clindamycin as an adjunct antibacterial; and avoidance of nonsteroidal anti-inflammatory drugs (NSAIDs). Hyperbaric oxygen therapy has been proposed in the management of necrotizing fasciitis but its benefit is unproven and is not discussed further.[105]

5.1 Supportive Care

Toxic shock syndrome is characterized by profound hypotension caused by toxin-mediated capillary leak. A full discussion of the intensive care management is beyond the scope of this review, but a number of key points are worthy of mention. Management of the capillary leak requires volume expansion and aggressive fluid replacement, and inotropes are often required early. Renal support may also be required early and it is important to recognize that renal failure may precede hypotension.[106] Patients frequently require endotracheal intubation and ventilation, particularly when ARDS develops.

5.2 Antibacterial Therapy

Penicillin is the first-line antibacterial of choice for invasive GAS disease. Isoxazole penicillins (cloxacillin, dicloxacillin, flucloxacillin) are also effective anti-streptococcal antibacterials and should be used when *S. aureus* cannot be excluded as a possible causative organism, as is usually the case. In areas where community-associated methicillin-resistant *S. aureus* infections are common, consideration should be given to broader Gram-positive cover such as vancomycin. In some cases of necrotizing fasciitis when differentiation of Type I from Type II is not initially possible, broad spectrum antibacterials to cover Gram-negative bacteria and anaerobes may be necessary.

Clindamycin is a useful and important adjunctive antibacterial in cases of STSS and severe GAS infection, especially necrotizing fasciitis. Clindamycin is a lincosamide antibacterial that 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.[91,107,108] In contrast to penicillin, clindamycin is not susceptible to the Eagle effect.[109] It also has direct effects on toxin production,[110-112] an ability to potentiate phagocytosis,[113] a longer post-antibiotic effect[114] and superior tissue penetration. Clindamycin should be used as an additive antibacterial not as a replacement for penicillin.[109] Clindamycin should be administered early in addition to a β-lactam. While clindamycin has been associated with severe *Clostridium difficile* infection, especially in elderly patients, its potential benefits in STSS and necrotizing fasciitis outweigh the risks.

5.3 Removal of Infected Tissue

Removal of any source of infection is critical in the early management of invasive GAS disease. Pus must be drained from sterile sites such as infected joints in the case of septic arthritis or from the pleural space in the case of empyema. Surgical management is crucial in cases of necrotizing fasciitis, and wide and early debridement of nonviable tissue is often necessary.[115] In one retrospective survey of adult patients with necrotizing fasciitis, patients who had early debridement had a lower mortality rate (4%) than those with late debridement (38%).[116] Some experts argue that the necessity for aggressive debridement can be

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avoided by the early use of IVIG, making it possible for a more conservative surgical approach to be effective.[117,118] As menstrual-related (usually staphylococcal) toxic shock syndrome may be indistinguishable from STSS, a search for and removal of any retained tampon is a critical part of the initial management.

5.4 Immunoglobulin Therapy

While IVIG is advocated for use in a number of sepsis syndromes, there is conflicting evidence about the effect of IVIG in lowering mortality in sepsis.[119,120] STSS may be one exception, where there is better evidence to support a role for IVIG. Laboratory evidence in favour of the use of IVIG in STSS includes the presence of neutralizing antibodies to streptococcal superantigen toxins in IVIG.[121] In addition, plasma from patients with STSS who have been treated with IVIG can inhibit superantigen-induced T-cell proliferation and production of cytokines *in vitro*.[122,123] IVIG has multiple other anti-inflammatory properties and the specific mechanism underlying its potential beneficial effect in STSS is unknown. Three clinical studies have investigated the benefit of IVIG in STSS (table III).[124-126] The first was an observational cohort study using historical controls that found that mortality at 30 days in patients administered IVIG was half that of control patients.[125] Of note, the case fatality rate in both groups was considerably higher than that generally seen today. A randomized controlled trial followed this study, but was ceased prematurely because of slow patient enrolment. This second study found a trend towards improved survival at 28 days in patients with STSS, but this finding was not statistically significant. A third, retrospective, study investigated outcomes in 182 children with STSS in selected parts of the US between 2003 and 2007. There was no difference in mortality between children who received IVIG (mortality 6.0%) and those who did not (mortality 2.8%; $p = 0.3$).[126] However, this study suffered from selection bias as a result of its retrospective design (the most unwell children received IVIG),[126] and expert commentators concluded that the available evidence still supports the use of IVIG in both adults and children with STSS.[127] The lower mortality of STSS in children compared with adults means that a randomized controlled trial of IVIG in children is unlikely to be conducted.[127] The use of IVIG needs to be weighed against its cost and potential adverse events, including immune-mediated haemolysis and anaphylaxis.[128]

5.5 Nonsteroidal Anti-Inflammatory Drugs

Some experts recommend the avoidance of NSAIDs in patients with invasive GAS disease. However, the association between the use of NSAIDs and necrotizing fasciitis and STSS is controversial.[56,129-134] A number of case reports as well as a case control study have noted an association between the use of NSAIDs and necrotizing fasciitis and STSS.[39,56,129,135-137] This association may simply be explained by NSAIDs leading to delayed presentation by masking fever and reducing pain. However, a biological mechanism has been proposed whereby NSAIDs inhibit the normal feedback loop of prostaglandin on the production of tumour necrosis factor (TNF)-α by macrophages, and also suppresses neutrophil function.[131] Some experts recommend therefore avoiding NSAIDs in patients with fever without a known source.[129,131] It is prudent to avoid NSAID use in patients with varicella, because of the known association between varicella infection, GAS infection and STSS, as previously outlined.[130]

Table III. Summary of results of three studies of intravenous immunoglobulin in streptococcal toxic shock syndrome

Study, year of publication	Type of study	Endpoint	IVIG group (%)	Placebo/control group (%)	p-Value
Darenberg et al.,[124] 2003	Randomized controlled trial	Mortality at 28 d	1/10 (10)	4/11 (36)	0.3
Kaul et al.,[125] 1999	Historically controlled observational study	Mortality at 30 d	7/21 (33)	21/32 (66)	0.02
Shah et al.,[126] 2009	Retrospective cohort study	Mortality	5/84 (6.0)	3/108 (2.8)	0.3

IVIG = intravenous immunoglobulin.

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6. Contact Prophylaxis

There is a known increased risk of secondary attacks in close contacts of cases of invasive GAS disease, analogous to meningococcal disease. Outbreaks of invasive GAS infections within family clusters, school children and communities are well described,[138-143] and these are characterized by the rapid spread of virulent clones among close contacts. Of the studies that have tried to systematically identify paired household cases, only ten pairs have been identified to date, one from the US, four from Canada and five from the UK. As such, there is a considerable margin of error in estimating secondary household risk.[44,66,144,145] In a study in Ontario, the attack rate for household contacts of patients with invasive GAS disease was 294 per 100 000 compared with the incidence of sporadic disease in the same population of 2.4 per 100 000.[44] The attack rate in a study in the US for household contacts of patients with invasive GAS disease was 66 per 100 000 compared with the incidence of sporadic disease in the same population of 3.5 per 100 000.[146] Estimation of attack rate from the UK cases was hampered by the absence of information on the number of household contacts, but on the basis of estimated household size, the increased risk ranged between 80 and 120/100 000 compared with a background risk of 3.85/100 000.[144]

Given the differences in these risk estimates and uncertainties over whether prophylaxis actually prevents secondary cases, different countries have adopted different recommendations.[147,148] The Canadian public health authorities recommend contact prophylaxis of close contacts, whilst the US Centers for Disease Control and Prevention recommends against prophylaxis unless a member of the household has an additional condition placing them at increased risk of infection. In contrast, UK guidelines have been influenced by the observation that, of the five paired cases of invasive GAS disease in the UK in 2003, three were mother-neonate pairs, and only one of the other two pairs could have been prevented (one pair presented almost simultaneously). Therefore, UK public health authorities have limited their recommendations for routine contact prophylaxis to postpartum mothers or their babies should the other develop invasive disease.[66] Of note, all three guidelines recommend treatment of close contacts if they have symptoms suggestive of localized GAS infection, that is sore throat, fever and/or skin infection. Advantages of contact prophylaxis include potentially preventing disease in contacts and transmission of virulent strains. The disadvantages include the unnecessary use of antibacterials in most contacts and the risk of side effects, including anaphylaxis.

Whereas the risk of secondary transmission for community-acquired cases is relatively low, the risk in hospital and long-term care facilities is considerably higher. A study from Canada found that one in ten invasive cases acquired in hospital occurred as part of an outbreak.[149] When hospital outbreaks occur, they can escalate rapidly, be prolonged and result in infections in both patients and healthcare workers.[149] As a result, several countries have developed guidance on the control of GAS infections in hospital.[146,150-152]

7. Conclusions

Invasive GAS infections are severe and often life threatening. Patients with invasive GAS infection are at risk of developing STSS, a superantigen-mediated clinical syndrome. STSS carries a high risk of mortality and is associated with necrotizing fasciitis. It is likely that there is a large burden of invasive GAS disease in many tropical developing countries, although data are lacking. The available evidence supports the need for early institution of supportive care, broad empiric antibacterial therapy until the diagnosis of GAS infection is made, the use of clindamycin because of its anti-toxin capacity, the early administration of IVIG especially if there is evidence of STSS, and debridement of necrotic tissue in cases of necrotizing fasciitis. In terms of therapeutic advances, it is unlikely that randomized controlled trials of treatment for invasive GAS infections will be conducted in the future.[124] However, large-scale observational and case control studies may provide evidence of the effectiveness of some interventions.

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Acknowledgements

The authors of this work have no conflicts of interest or funding to disclose.

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