Invasive Group B Streptococcal Disease in Non-pregnant Adults

A Review with Emphasis on Skin and Soft-tissue Infections

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Abstract

Streptococcus agalactiae, commonly referred as group *B Streptococcus* (GBS), is a major cause of neonatal sepsis and infections in pregnant women. However, the number of invasive infections in non-pregnant adults is growing. Elderly patients and those with chronic underlying conditions, such as diabetes mellitus or compromised immune defence, are at increased risk of invasion. The spectrum of clinical manifestations is broad and includes necrotizing fasciitis and toxic shock syndrome. Although, primary bacteremia and skin and soft-tissue infections are the most frequently reported diagnosis. This article reviews the epidemiology, pathogenesis and treatment of invasive GBS disease in non-pregnant adults, with an emphasis on skin and soft-tissue infections.

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Introduction

Streptococcus agalactiae is the only streptococcal species that carries the Lancefield group B antigen, hence its alternative designation as group B *Streptococcus* (GBS). It is a leading cause of morbidity and mortality in neonates and pregnant women. In many industrialized countries, recommendations for diagnosing maternal GBS colonization and administering intrapartum antimicrobial prophylaxis have been introduced, leading to a significance decrease in these infections [1]. However, the rate of invasive GBS disease in non-pregnant adults continues to climb [2]. Elderly persons and those with underlying diseases – two expanding segments of the population – are at increased risk. This article reviews the epidemiology of invasive GBS disease in non-pregnant adults, describes clinical, immunological and bacterial perspectives of its pathogenesis, and discusses treatment concepts for this condition. Emphasis is placed on skin and soft-tissue infections, which are among the most frequently reported clinical problems.

Epidemiology

Incidence of Invasive Group B Streptococcal Disease

In the early 1990s, three large surveillance studies in the United States reported a significant increase over the previous two decades in the annual incidence of invasive GBS disease (defined as isolation of *S. agalactiae* from a normally sterile site [3]) among non-pregnant adults. The rates had reached 2.4–4.4 cases per 100,000 population [4–6]. Thereafter, several reports revealed an increase in incidence of both invasive diseases and bacteremia per 1000 hospital admissions [2, 7]. Recent studies have reported an annual incidence of invasive GBS disease of 0.96 (Spain) or an incidence of GBS bacteremia of 0.136 (Hong Kong), 0.30 (Taiwan) and 0.42 (Spain) cases per 1000 hospital admissions, which also illustrate regional differences [7–9]. This trend can be partly explained by a growing number of patients with predisposing factors, in particular, chronic medical conditions.

Relapsing Infections

Approximately 5% of non-pregnant adults will have at least a second episode of GBS disease. In the study by Harrison et al. [10] the interval between the first and second episode averaged 13 weeks if the bacteremia was caused by the same strain and 43 weeks if it was caused by a different strain. In this study, all infections occurred in patients with predisposing conditions, and cellulitis was the most frequent recurrent clinical manifestation.

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Predisposing Conditions and Risk Factors

The vast majority of patients with GBS infections have at least one predisposing condition. Important risk factors and their calculated incidence rates are presented in table 1. Older age (> 65 years), diabetes mellitus, cancer and compromised immunity are recognized to increase the risk of acquiring invasive GBS disease [2, 4, 6, 11]. Venous oedema and/or lymphoedema have been determined as risk factors for relapsing erysipelas/cellulitis of the lower leg [12]. However, in a retrospective study analysing 71 patients suffering from GBS skin and soft-tissue infections [13], 17 (24%) had no obvious underlying disease. This percentage is higher than those previously reported, ranging between 0–8% [2, 4, 6, 7, 14–17]. Nevertheless, it emphasizes that GBS is not exclusively affecting risk groups.

Since, like all patients, GBS-colonized individuals are exposed to various instrumentation techniques (e.g. urinary catheter, sigmoidoscopy), this iatrogenic factor may be contributing to the incidence rate [18, 19]. In one-quarter (17–30%) of the cases, invasive GBS disease occurs ≥ 48 hours after admission to a hospital [6, 11, 20]. Nosocomial infection may therefore arise from pre-existing colonized skin or mucosal surfaces.

Prevalence of GBS Colonization

In colonized individuals, GBS is generally isolated from cultures of the rectum, perianal area, vagina, cervix and urethra or, less commonly, from cultures of the skin and pharynx. The colonization rate ranges from 20 to 35% [21–26]. The prevalence is higher among sexually active persons and those who have multiple sex partners, suggesting that acquisition of this microorganism is caused by intimate contact [23, 27]. This is also supported by a study showing identical strains in 86% of co-colonized sex partners [21].

Serotype Distribution

GBS expresses a polysaccharide antigen on its surface that is used for serotype identification. To date, nine serotypes have been identified: Ia, Ib and II–VIII [28]. Characterization of a GBS strain also includes the presence of surface proteins. The C-protein complex, which consists of two independently expressed components (the α- and β-antigen), is among the best-studied of these surface proteins.

Most of the epidemiological data on GBS serotypes have been collected from strains causing invasive disease. In non-pregnant adults, almost 70% of the invasive cases have been attributed to serotypes Ia, III and V [29–31]. These three serotypes also dominated in a study analysing colonizing strains in healthy elderly persons [26]. C-protein antigens are found in 40–60% of clinical isolates, mostly in strains with serotype Ia, Ib and II [28, 32]. However, the serotype distribution has shifted somewhat during the past few years [33]. Pregnant Japanese women were found to be predominantly colonized with serotypes VI and VIII [34], whereas invasive disease was being increasingly caused by serotype VIII in a Danish study [35]. Whether this difference is due to geographic predominance or due to the type of infection remains to be determined. However, the serotype distribution of both invasive and colonizing

Table 1
Underlying conditions associated with an increased risk for acquiring GBS infections in non-pregnant adults.

Study design, study population, number of patients	Predisposing condition	Incidence of invasive infection[a]	Risk calculation (95% CI)	
			Relative risk	Odds ratio
Retrospective population-based surveillance, non-pregnant adults, 56 [4]	Diabetes mellitus	13.7	10.5 (7.8–14.4)	–
	Cancer	21.3	16.4 (11.5–23.3)	–
Case-control study, non-pregnant adults, 219 cases and 645 hospital-matched controls [11]	Diabetes mellitus[b]	–	–	3.0 (1.9–4.7)
	Breast cancer[b]	–	–	4.0 (1.6–9.8)
	Liver cirrhosis[b]	–	–	9.7 (3.5–26.9)
	Neurogenic bladder[b]	–	–	4.6 (1.4–15.1)
	Decubitus ulcer[b]	–	–	4.0 (1.6–9.8)
	Stroke[b]	–	–	3.5 (1.9–6.4)
Prospective population-based surveillance, non-pregnant adults, 137 [6]	Diabetes mellitus (age 20–40)	20	30 (11–79)	–
	HIV (age 30–49)	54	30 (11–78)	–
Active bacterial core surveillance[c] The surveillance areas represented 27,350,255 persons [3]	Age > 65	25.6	–	–
Active surveillance, non-pregnant adults, 867 cases including 84 nursing home residents [134]	Nursing home residents age ≥ 65	–	4.1 (2.6–6.7)[d]	

[a]Annual incidence of invasive GBS infection per 100,000 population; [b]Multivariate analysis [11] adjusted for age, diabetes mellitus, breast cancer, liver cirrhosis, neurogenic bladder, decubitus ulcer, stroke, congestive heart failure, dementia, incontinence, gastrointestinal bleeding, alcoholism and prostate cancer; [c]CDC = Centers for Disease Control (USA); [d]Compared to selected community residents (age ≥ 65)

strains is continuously evolving and demonstrates not only regional but also temporal variation.

Macrolide- and Clindamycin-resistant Strains

There is significant and rising resistance to erythromycin and clindamycin in both invasive and colonizing strains [36]. Reported frequencies range from 7 to 16% and 3 to 9%, respectively [36, 37], although there are geographic variations in resistance rates and prevalence of resistance mechanisms. High rates of erythromycin and clindamycin resistance have, however, only been rarely reported: in one study testing 200 GBS isolates collected from vaginal/rectal specimens [38], the resistance rate was 54% and 33%, respectively.

Among erythromycin-resistant isolates, several studies have reported serotype V as the most frequent serotype [39–43].

Challenges in Detecting GBS

Detailed routine diagnostic methods have been described elsewhere and are beyond the scope of this review [44, 45]. However, clinicians should be aware that apart from the commonly known phenotype with a narrow zone of haemolysis on a blood agar plate, an unknown percentage of the strains are either non-hemolytic or hyperhemolytic. Non-haemolytic strains are non-pigmented, while hyperhemolytic strains are hyperpigmented [46]. Non-hemolytic strains can be missed when strains are not screened for the group B antigen. Furthermore, in screening procedures for carrier status, low colonization levels, the presence of other organisms (e.g. in a vaginal culture) and low test sensitivity of the commercial assays pose problems in identifying GBS. Therefore, the detection of GBS isolates and the interpretation of culture results, both from colonized individuals and patients suffering from invasive disease, require a good collaboration between clinicians, microbiologists and laboratory technicians.

Pathogenesis — the Clinical Perspective

According to the traditional concept, a clone of GBS is entering normally sterile sites such as blood or cerebrospinal fluid after pre-existing or new colonization of the host [47]. This model is supported by two recently published case reports, showing identical strains isolated from the vagina and the blood [48, 49].

The integrity and functionality of the mucosa and skin represent the first line of host defence. Alteration of these barriers allows the pathogen to escape from its reservoir and cause invasive disease. Chronic medical conditions typically known to be associated with skin alterations (e.g. diabetes mellitus, peripheral vascular diseases, pressure ulcers) or mucosal lesions (e.g. ulcer disease, HIV) enhance the risk of invasive disease. Lymphatic or vascular insufficiency, a history of radiation therapy or chronic dermatological diseases are often present in skin and soft-tissue infections [12, 49, 50]. As a typical example of such a predisposing constellation to GBS infection, arm and chest wall cellulitis have been reported in patients with a history of breast cancer that has included surgical and radiation therapy [6, 11, 48].

In relapsing diseases, focal infections such as endocarditis or osteomyelitis that may have been unrecognized during the fist episode must be excluded [10]. Persistent gastrointestinal or genitourinary carriage of a certain GBS strain to which the host is susceptible (due to the pathogen's virulence, or to the host's immune status, or both) may serve as a reservoir for relapsing invasive diseases [48, 49]. Another possibility includes repetitive acquisition of matching strains from intimate contact with a GBS carrier. Bacterial persistence at the local site of infection has been also speculated as a cause of recurrent skin and soft-tissue infections [49]. In relapsing cellulitis, often observed as a chronic complication after surgery, lymphatic tissue is altered and may lead to locally impaired immune responses and insufficient bacterial clearance [12, 48, 51]. The observation of intracellular persistence in host cells could also help to explain relapsing infections; through this strategy, bacteria may escape common extracellular immunological mechanisms as well as bactericidal concentrations of antibiotic. Intracellular persistence in non-professional phagocytes and in macrophages has been shown in patient material with *Staphylococcus aureus* [52] and Group A *Streptococcus* (GAS) [53] infections, respectively.

Pathogenesis — the Immunological Perspective

The role of type-specific anti-GBS antibodies has been primarily investigated in neonates and pregnant women. Serum analyses of neonates (and their mothers) suffering from systemic GBS serotype III infection have shown low titres of type-specific antibodies directed against the capsular polysaccharide (CPS) [54]. Clinical data to confirm the hypothesis that type-specific antibodies may play an important role in protecting non-pregnant adults from invasive disease are sparse. Several studies have tested GBS conjugate vaccines in healthy young adults and investigated the functional activity and the concentration of the induced antibodies [55–57]. They showed a significant positive correlation between the concentration of CPS-specific antibody in the serum and opsonophagocytic activity.

Functional assays in elderly persons may partially explain why this group is more susceptible to invasive GBS disease. In a cross-sectional study with healthy elderly people [58], impaired GBS killing was associated with a low concentration of CPS-specific antibodies [58]. The addition of pooled sera from young adults vaccinated against type V GBS improved impaired neutrophil-mediated phagocytosis. Similarly, type V vaccination of healthy elderly adults induced normal, functional antibodies that promoted opsonophagocytic killing *in vitro* [59]. Taken together, these data suggest that CPS-specific antibodies may play an important role in the immune defence

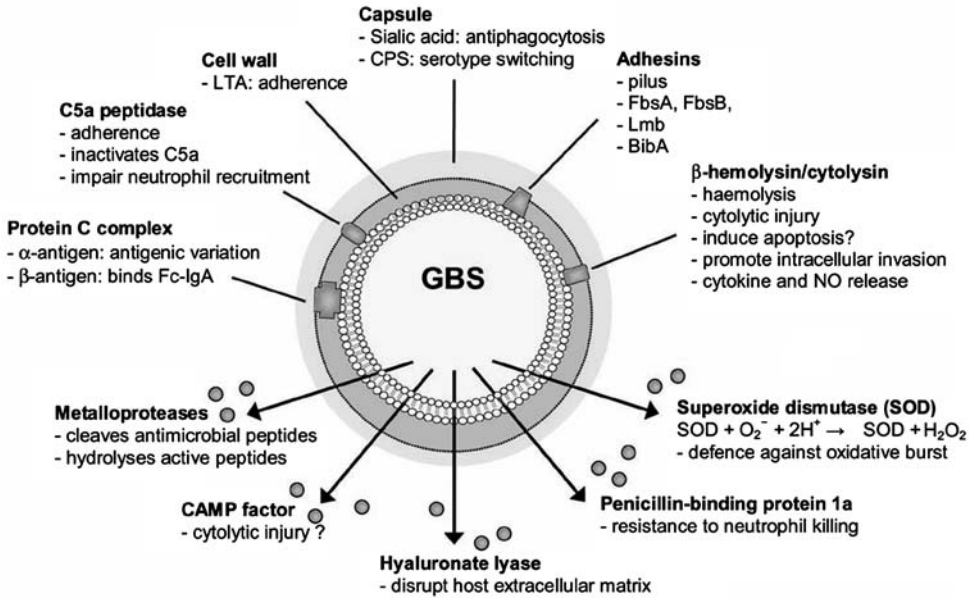

Figure 1. Schematic overview of GBS factors involved in adhesion, invasion, avoidance of immune clearance and virulence. The list of bacterial features shown is not exhaustive and additional findings are being continuously reported in the literature. LTA: lipoteichoic acid; CPS: capsular polysaccharide antigen, Fbs: fibrinogen-binding protein; Lmb: laminin-binding protein; BibA: B Streptococcus immunogenic bacterial adhesion.

of non-pregnant adults, although the clinical significance of these results is difficult to assess. They also indicate that due to limitations of factors other than immunoglobulins in the host defence of the elderly, higher concentrations of CPS-specific antibodies might be required to confer protection [47].

Similar conclusions can be drawn from studies in diabetics, who are generally more prone to bacterial infections. In assays using serum samples from persons with insulin-dependent diabetes, poor opsonophagocytosis to type II GBS improved following the addition of CPS-specific antibodies [60]. Furthermore, neutrophils obtained from elderly adults with type 2 diabetes showed diminished superoxide production during hyperglycaemia when stimulated with GBS type III. Improvement of the oxidative burst was shown in the presence of a higher CPS-specific IgG concentration [61].

Pathogenesis — the Bacterial Perspective

Detailed elucidation of the bacterial pathogenesis in humans poses several problems. GBS adapts to its host during the process of colonization and expresses host-specific surface proteins, some of which are only expressed in the host and not in laboratory cultures. Nevertheless, much research effort has been successfully devoted to pathomechanisms of GBS diseases and has identified a large number of important bacterial components involved in adhesion, invasion, avoiding immune clearance and causing inflammation (schematically in figure 1). Several of these bacterial features occur via a 'two-component regulatory system'. One component (e.g. a sensor protein) is responsible for detecting and communicating the external stimuli, while the other component (e.g. regulator protein) will react to those signals by activating or repressing specific genes, leading to the appropriate bacterial functions [62]. This system has been recognized as a bacterial strategy to overcome environmental stress factors, such as pH, temperature and osmolarity [63], but also to adhere to host cells [64, 65] and to express virulence factors [66].

Adhesion and Invasion

GBS interacts with extracellular matrix components of eukaryotic host cells, such as fibronectin, fibrinogen, laminin and cytokeratin 8. Several GBS surface-associated factors have been implicated in the adhesion process (Figure 1). Once adhered, GBS is able to invade eukaryotic cells, such as fibroblasts, endothelial and epithelial cells, thus promoting bacterial penetration of host cellular barriers, such as the blood-brain barrier [67], chorioamniotic membranes [68] or barriers in the respiratory tract [69].

Avoidance of Immune Clearance

Apart from adaptation to environmental stress factors, GBS displays several functions that provide protection against killing by the host's immune system. On mucosal surfaces, GBS binds the Fc fragment of IgA via a surface-associated protein complex (β-antigen of protein-C) [70] and thus inhibits interaction of IgA with Fc receptors expressed on neutrophils, eosinophils or macrophages [71].

GBS possesses also several mechanisms to resist opsonophagocytosis. Sialic acid, a component of the capsule,

prevents deposition of active C3b, and thus its function as an opsonin [72]. C5a, another important factor of the complement system that acts as a chemotaxin for neutrophils, can also be inactivated by a surface-bound streptococcal protease, namely C5a peptidase [73]. Other factors that endow GBS with resistance to phagocytic killing by neutrophils includes its penicillin-binding protein 1a, metalloproteases and superoxide dismutases (Figure 1) [74, 75]. Further strategies that have been suggested for how the microorganism avoids opsonization by antibodies include antigenic variation of a surface-associated protein complex (the α-antigen of the protein C) [76] and capsular serotype switching [77]. Also, intracellular survival in macrophages has been demonstrated *in vitro* [78], by a mechanism that presumably impairs activation of the host cell.

An offensive mode used by GBS to evade the host immune system is its ability to induce apoptosis in monocytes and macrophages [79]. Experimental data suggest that apoptosis is induced by β-haemolysin/cytolysin (β-h/c), a surface-associated toxin [80], although the detailed pathogenesis that triggers apoptosis is not yet fully understood.

Virulence

Several virulence factors have been identified in GBS, which contribute significantly to tissue damage at the local site of infection, as well as to a systemic inflammatory response by the host.

The capsule, a relatively unstructured network of high-molecular-weight polymers, is considered to be a major virulence factor. An overwhelming majority of GBS isolates from invasive disease are encapsulated. In animal experiments, non-encapsulated isogenic mutants demonstrated significantly reduced virulence compared to the corresponding wild-type strain [81].

The already mentioned surface-associated β-h/c is a potent, oxygen-stable, non-immunogenic GBS toxin, comparable to streptolysin S of GAS [82]. In addition to its hemolytic activity, β-h/c is responsible for pore formation and cytolytic injury to fibroblasts, endothelial and epithelial cells, as well as for promoting intracellular invasion, cytokine and nitric oxide release and, consequently, for triggering the sepsis cascade [80, 83]. Its expression has therefore been correlated with the severity of disease and tissue damage [84].

The CAMP factor has also been shown to have pore-forming activity, but this function is mainly seen on red blood cells pre-treated with sphingomyelinase (produced by *S. aureus*) [85]. Whether this factor plays a role in polymicrobial infections involving both GBS and *S. aureus* has not yet been assessed.

GBS is equipped with multiple oligopeptidases that promote the hydrolysis of several active peptides (or their fragments), such as bradykinin, the neuropeptides neurotensin and substance P, and adrenocorticotropin [74]. The biological function of these pathomechanisms is not known, but peptide degradation in the tissue surroundings of GBS has been speculated in meningitis cases.

In GAS, superantigens have been implicated as major mediators of systemic toxicity and tissue damages. In GBS, though, most studies have failed to demonstrate exotoxins with superantigen activities. However, a recent case report described a GBS toxic shock-like syndrome, in which further experiments with human peripheral mononuclear cells and the isolated strain demonstrated superantigenic stimulation [86]. Also, *Schlievert* et al. [87] purified a protein from a GBS strain that had the biological activities of a pyrogenic toxin. Whether a horizontal transfer of DNA encoding such a virulence factor is occurring between different GBS strains, as has been shown for GAS [88], remains to be proven; there are, nevertheless, convincing indications for this hypothesis, in particular for genes encoding certain GBS surface proteins (α-antigen of protein C, C5a peptidase, Lmb protein) [89]. It is therefore plausible that such a mechanism is contributing to an increased incidence of severe diseases [90–92].

Macrolide Resistance

The mechanisms are mainly based on efflux pumps transporting macrolides out of the bacterial cytoplasm or on ribosome modifications that alter the antibiotic target site. The efflux pump is encoded by the *mefA* gene, whereas the acquisition of *ermB* and/or *ermTR* (*e*rythromycin *r*ibosome *m*ethylase) genes confers a ribosomal modification. *erm* genes are associated with macrolide-lincosamide-streptogramin B (MLS_B) resistance and can be expressed constitutively ($cMLS_B$) or upon induction ($iMLS_B$), although there is a heterogenic distribution of *erm* genes among these phenotypes [39]. Several studies have indicated how macrolide resistance might be acquired. A comparative pulsed-field gel electrophoresis analysis showed genetic clustering among macrolide-resistant GBS strains, with the predominance of a single-clone family within an otherwise heterogeneous serotype V population [40]. Based on these data, the emergence of a specific macrolide-resistant clone family that possibly acquired resistance at a certain point of evolution and then subsequently increased in numbers was suggested. Recently, *Puopolo* et al. [93] found that the *ermB* gene is present on the chromosome of GBS within a transposon similar to the one identified in *Streptococcus pneumoniae*, which possibly indicates the horizontal transfer of such a mobile transposable element among streptococci.

Clinical Manifestations

GBS may occur in a large variety of clinical manifestation, as presented in table 2. Bacteremia without identified source and skin and soft-tissue infections are the most frequently reported expressions of invasive GBS disease

Table 2
Relative frequency of different clinical manifestations of invasive GBS infections in non-pregnant adults.

Disease	Median % (IQR)
Bacteremia with unknown source	24 (4–40)
Skin and soft-tissue infections	20 (12–36)
Respiratory infections	12 (3–19)
Genitourinary infections	10 (0–20)
Joint and bone infections	8 (4–19)
Abdominal infections	5 (0–10)
Endocarditis	4 (0–13)
Infections of the central nervous system	4 (0–7)
Miscellaneous	< 1 (0–12)
-Intravascular-device infections	
-Ear, nose and throat infections	
-Endophthalmitis	
-Iatrogenic (e.g. post-endoscopy)	
-Others	

Analyses are based on 20 studies including 1167 episodes of invasive GBS infections [2, 4, 6, 7, 9, 11, 14–17, 20, 94, 131–133, 135–139]; IQR: interquartile range

in non-pregnant adults. In up to one-third of the cases, in particular in skin and soft-tissue diseases, the pathogen is involved in a polymicrobial infection [2, 6, 7, 11, 13, 15, 16, 94]. In such situations, *S. aureus* is the most frequently isolated co-microorganism.

Skin diseases typically present as erysipelas/cellulitis, infected wounds or ulcers. However, GBS can also cause myositis, necrotizing fasciitis and toxic shock syndrome.

Infected Skin Ulcers

Physical defence factors and mechanical barriers are impoverished in ulcers and wounds, facilitating the invasion of GBS. Not surprisingly, the presence of decubitus ulcers has been associated with an increased risk for invasive GBS disease (Table 1) [11]. In patients with diabetes mellitus and foot ulcers, apart from *Staphylococcus* spp., GBS is the most frequently involved pathogen among isolated Gram-positive bacteria [95]. In diabetic foot infections, it is important to rule out osteomyelitis and to distinguish between colonizing and infecting pathogens by culturing biopsies.

Erysipelas and Cellulites

In both entities, skin lesions are frequently considered to be a portal of entry. Cellulitis is the most reported diagnosis among GBS skin and soft-tissue infections (25% in one study) [13, 47]. However, since aetiologic organisms are only rarely isolated (positive blood cultures in 2–5% of cases) [96, 97], the true incidence might be underestimated. Thus, in patients suffering from cellulitis by an unidentified pathogen and with known risk factors and/or carrier status, GBS should be considered.

Necrotizing Fasciitis

This severe infection has been categorized into two types. Type I is usually a polymicrobial infection (including anaerobic bacteria) that is associated with antecedent surgery, diabetes mellitus and vascular diseases, and manifests clinically with destruction of fat and fascia. Type II is monomicrobial, typically but not exclusively caused by GAS, and occurs commonly in patients without underlying diseases; it often presents with severe local pain, rapidly extending necrosis of the subcutaneous tissue and systemic toxicity. GBS as the

Table 3
Streptococcal toxic shock syndrome case definition.

Community-acquired case: An illness with the following clinical manifestations occurring within the first 48 hours of hospitalization
Nosocomial case: An illness with the following clinical manifestations occurring within the first 48 hours of illness
Clinical criteria:
- Hypotension : Systolic blood pressure $\leq$ 90 mmHg
- Multiorgan involvement characterized by two or more of the following:
  1. *Coagulopathy*: Platelets $\leq$ 100,000/mm^3 ($\leq$ 100 x 10^6/L) or DIC
  2. *Renal impairment*: Creatinine $\geq$ 2 mg/dL ($\geq$ 177 μmol/L)
  3. *Liver involvement*: ALAT, ASAT, total bilirubin levels $\geq$ twofold the upper limit of normal for the patient's age. In patients with preexisting liver disease, a greater than twofold increase over the baseline level
  4. *Lung:* ARDS
  5. Skin: A generalized erythematous macular rash that may desquamate
  6. Soft-tissue: Necrosis, including necrotizing fasciitis or myositis, or gangrene

Laboratory criteria:
- Isolation of GAS

Diagnosis:
Probable STSS: clinical case definition + isolation of GAS from a non-sterile site[a]
Confirmed STSS: clinical case definition + isolation of GAS from a normally sterile site

Adapted from CDC case definition 1996 [107].
[a]In the absence of another identified aetiology for the illness; GAS: Group A *Streptococcus*; DIC: disseminated intravasal coagulation; ASAT: aspartate aminotransferase; ALAT: alanine aminotransferase; ARDS: acute respiratory distress syndrome

causative pathogen has been rarely reported, but the number of cases in the literature, both in type I and II fasciitis, is steadily increasing [7, 9, 13, 50, 90–92, 98–104]. It has been suggested that GBS necrotizing fasciitis in non-pregnant adults tends to occur in patients with significant underlying diseases [90], but this relationship is difficult to support by data due to the rarity of the disease. Moreover, cases in patients without risk factors have been reported [91, 100, 101].

Analyses of GBS serotypes and several virulence factors in a case series have not elucidated why some patients develop necrotizing fasciitis and others develop both necrotizing fasciitis and toxic shock syndrome [92]. Similarly, host genetic factors that may contribute to the development of GBS toxic shock syndrome or necrotizing fasciitis are as yet undetermined. Genetic predisposition has been demonstrated in invasive GAS infections: specific haplotypes of class II human leukocyte antigens (HLA) conferred protection against severe systemic disease, while certain haplotypes were found to be associated with the development of necrotizing fasciitis and others with that of toxic shock syndrome [105].

Toxic Shock Syndrome

Streptococcal toxic shock syndrome (STSS) is defined as an acute and febrile illness that begins with mild viral prodromi but rapidly progresses to shock and multiorgan failure (Table 3) [106, 107]. Although STSS is classically associated with GAS, there is an increasing recognition that other streptococci, i.e. Groups B, C and G, can be the causative pathogen [108–111].

Group B STSS cases are often associated with severe skin infections [90–92, 99, 100, 112]. Comparison of the clinical characteristics of STSS caused by GAS and GBS in non-pregnant adults is statistically difficult, mainly because the distribution of incidence numbers is unequal. However, there is tendency for a lower GBS frequency in adults below 50 years of age, irrespective of the presence of underlying disease [87, 91, 92, 100, 103].

Medical Treatment

Clinical isolates of GBS are susceptible to penicillin, the antimicrobial agent of choice for treating these invasive diseases [36]. In a European inter-country comparison, the average MIC was 0.06 mg/L (broth microdilution assay) and 0.09 mg/L (Etest) [113]. These values are two- to ninefold higher than those for GAS. The occurrence of penicillin tolerance in clinical GBS isolates varies among different studies, ranging from 5% to 15% [114]. This *in vitro* phenomenon is observed when bacteria are inhibited by low concentrations of penicillin but are killed at much higher concentrations (MBC/MIC-ratio ≥ 1/32).

GBS strains are also susceptible to ampicillin, ceftriaxone, cefotaxime, meropenem, levofloxacin and vancomycin [36, 41]. As mentioned above, erythromycin and clindamycin resistance is rising. Strains demonstrating resistance to macrolides should be tested for MLS_B resistance, in particular, when considering clindamycin treatment [115].

Aminoglycosides alone have little or no effect on GBS, but synergistic killing with penicillin has been shown *in vitro* [116]. These results have been extrapolated in therapeutic strategies for severe sepsis cases and for isolates with penicillin tolerance or with high MIC values (e.g. > 0.1 mg/L). However, there is increasing solid evidence, though more for Gram-negative than for Gram-positive pathogens, that the addition of an aminoglycoside to a β-lactam is not beneficial in sepsis and carries the risk of nephrotoxicity [117]. The clinical significance of a penicillin-aminoglycoside combination for penicillin-tolerant strains has not yet been established. Moreover, GBS high-level gentamicin resistance, leading to a lack of synergistic effect, has been also described [118]. Nevertheless, the addition of an aminoglycoside to penicillin might be considered in selected cases.

There are no uniform treatment recommendations for GBS skin and soft-tissue infections. Suggestions are mostly based on case reports, case series, clinical diagnosis or *in vitro* experiments. Practice guidelines published by the IDSA give a thorough overview for the management of skin and soft-tissue infections [119] and are likely also applicable to those caused by GBS. Most regimens for uncomplicated erysipelas/cellulitis include a 5- to 10-day course of antimicrobial treatment. However, based on the above-mentioned host risk factors for acquiring invasive disease, the ability of the pathogen to avoid immune clearance and the higher MICs compared to GAS, therapy for 10–14 days in GBS erysipelas/cellulitis might be considered [33]. Whether oral or intravenous therapy is adequate, and at what time parenteral antibiotics can be changed to oral therapy, should always be discussed.

In erysipelas, treatment with penicillin G (12–18 million units IV per day divided into four to six doses) or with a cephalosporin (e.g. ceftriaxone 2 g IV once daily) or vancomycin (15 mg/kg IV every 12 hours in penicillin-allergic patients with normal renal function) is commonly administered. Thereafter, systemic inflammatory response signs often resolve within 1–2 days, and treatment can be promptly switched to oral antibiotics. However, in a Swedish study including 60 episodes of erysipelas without previous treatment [120], oral therapy (with penicillin or clindamycin) had no inferiority in clinical course and outcome compared to intravenous treatment. Furthermore, penicillin V concentrations measured in punch biopsies from 45 orally treated patients with erysipelas exceeded the MIC of isolated streptococci [121]. Nevertheless, since penicillin MIC values of GBS are higher than those of GAS, and macrolide and clindamycin resistance is increasing, MIC testing can be helpful to evaluate treatment options.

In acute cellulitis, clinical presentation may require hospitalization and treatment with intravenous antibiotics.

Once GBS has been identified as the causative pathogen, antibiotic therapy should be streamlined accordingly. In clinical practice, intravenous treatment is generally switched to oral agents after the infected area has begun to improve (e.g. within 3–5 days). There are numerous agents available for oral therapy, as reviewed by *Jacobs* et al. [122]. Amoxicillin, among others, is effective in treating GBS cellulitis (2–3 g per day divided into two to three doses). Clindamycin (300 mg every 6–8 hours), or levofloxacin (500 mg once daily) are possible alternatives for patients with penicillin allergy.

Treatment of necrotizing fasciitis requires early and aggressive surgical exploration (debridement of necrotic tissue), antibiotic therapy and intensive care support. The duration of antimicrobial treatment is generally based upon clinical judgment [119]. In GBS necrotizing fasciitis, reported treatment durations from case series include 14–21 days intravenous antibiotics, followed by 14–21 days oral treatment [91]. As a part of the treatment concept, some authors have advocated the use of clindamycin (600–900 mg IV every 8 hours) in combination with penicillin (20–30 million units IV per day divided into four to six doses) in cases of GBS necrotizing fasciitis and/or STSS [90, 91, 99]. The efficacy of clindamycin is likely related to its ability to suppress the synthesis of GAS proteins, including M-protein and streptococcal pyrogenic exotoxins A and B [123]. Furthermore, the bactericidal effect of clindamycin is not dependent on bacterial growth stage or inoculum size; in contrast, these factors have been proposed as responsible for a decreasing killing rate of GAS at higher penicillin concentrations (''Eagle effect'') [124]. A population-based study of invasive GAS infections reported that clindamycin reduced mortality in patients who had necrotizing fasciitis [125]. On the other hand, in an *in vitro* time-kill study using clinically relevant antimicrobial concentrations, neither an antagonistic nor a synergistic effect of the penicillin-clindamycin combination was shown [126]. However, such data are largely lacking for GBS, and therefore recommendations for clindamycin in GAS necrotizing fasciitis cannot be simply applied to those of GBS.

The use of intravenous immunoglobulins (IVIG) in necrotizing fasciitis and STSS caused by GBS has not been evaluated, even though it has been administered in analogy to Group A STSS in selected cases [90, 91, 99]. Given the reports of a beneficial effect in STSS and in necrotizing fasciitis caused by GAS [127–129], together with the identification of a purified GBS toxin isolated from a patient suffering from STSS [86, 87], it is theoretically plausible to regard IVIG as an adjunctive treatment. However, no recommendation about the use of IVIG in GBS cases can be made at this time.

Patients with relapsing skin and soft-tissue infections and no identifiable source should be evaluated for a prophylactic course of antibiotics or for eradication of GBS carriage [119]. However, the most appropriate antibiotic regimen and the efficacy of such an approach are unknown for GBS. Options proposed for recurrent erysipelas/cellulitis [119] may be insufficient for those caused by GBS [48, 49, 130].

Outcome

During the last two decades, the mortality from invasive GBS disease has declined steadily, and is currently estimated at between 15–20%, with an attributable mortality of approximately 10% [2, 4, 6, 7, 9, 14, 15, 17, 94, 131–133]. As in other bacterial diseases, critical illness, in particular septic shock, at admission is strongly associated with increased mortality. Other factors associated with mortality include GBS bacteremia, diabetes mellitus, lung cancer, corticosteroid therapy, chronic renal insufficiency and congestive heart failure [7]. In GBS skin and soft-tissue infections, advanced age, skin ulcers and polymicrobial infections have been evaluated as risk factors for limb amputation [13]. The mortality rate of necrotizing fasciitis remains high, irrespective of the pathogen. In a series of 89 patients treated at a specialized center, the mortality was still 21.3% [98]. In these infections, rapid recognition and adequate surgical treatment have a significant influence on outcome. Group B STSS seems to have a similar outcome to STSS caused by GAS and other pathogens, even though the disease incidence is still too low for solid comparative studies [92].

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