

Streptococcus agalactiae Toxic Shock-Like Syndrome

Two Case Reports and Review of the Literature

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Abstract: We present 2 patients with *Streptococcus agalactiae* toxic shock-like syndrome and review another 11 well-reported cases from the literature. Streptococcal toxic shock-like syndrome is a devastating illness with a high mortality rate, therefore we stress the importance of early supportive management, antimicrobial therapy, and surgical intervention. Toxic shock-like syndrome is likely to be underestimated in patients with invasive *Streptococcus agalactiae* infection who present with shock. Early diagnosis requires high suspicion of the illness, along with a thorough mucocutaneous examination. *Streptococcus agalactiae* produces uncharacterized pyrogenic toxins, which explains the ability of the organism to cause toxic shock-like syndrome.

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Abbreviations: CT = computed tomography, GBS = group B streptococcus, LPS = lipopolysaccharide, MLS_B = macrolide-lincosamide-streptogramin B, SPE = streptococcal pyrogenic exotoxin, TSLS = toxic shock-like syndrome, TSS = toxic shock syndrome, WBC = white blood cell count.

INTRODUCTION

Streptococcus agalactiae, commonly referred as group B streptococcus (GBS), has been recognized as an emerging infection in nonpregnant adults with underlying medical conditions (mainly malignancy and diabetes mellitus).^{4,9,10,17,20,23,24,32,33,37} Several reports reveal a significant increase in the disease burden in adults, a trend that might be explained by a growing number of patients with chronic medical conditions.^{4,9,10,17,20,24,32,33,37} A 2009 multistate, population-based surveillance study³⁷ in the United States showed that the incidence of invasive GBS disease in nonpregnant adults doubled from 3.6 cases per 100,000 population during 1990 to 7.3 cases per 100,000 population in 2007. However, the risk is as high as 22–26 per 100,000 population among adults aged 65 years or older.^{24,37} The most prevalent GBS serotypes in nonpregnant adult infections are V, Ia, II, and III;

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these accounted for 78.5% of invasive GBS infections in 2005–2006.³⁷ GBS causes a broad spectrum of clinical manifestations; bacteremia and skin soft tissue infections are the most frequent expressions of invasive GBS disease in nonpregnant adults.^{35,37} The organism can also cause respiratory, genitourinary, joint, bone, abdominal, central nervous system, and endovascular infections.

Toxic shock syndrome (TSS) is an acute illness caused mainly by exotoxin-producing strains of *Staphylococcus aureus* and *Streptococcus pyogenes*. The exotoxins typically induce pyrogenicity and enhance the lethal effects of endotoxin (gram-negative lipopolysaccharide; LPS). They can activate the immune system, bypassing the usual antigen-mediated immune response sequence, resulting in the release of large quantities of inflammatory cytokines with consequent multiorgan failure.^{14,21,22} Group B streptococcus toxic shock-like syndrome (TSLS) is rare, and only a few cases have been reported in the literature. We report here 2 new cases of GBS skin soft tissue infection associated with TSLS. We performed a review of the available literature and report here an overview of current knowledge about the clinical characteristics and available treatments of GBS-induced TSLS. The other objective of this study was to test the isolated strains of GBS for known streptococcal pyrogenic exotoxins (SPEs) and undescribed pyrogenic toxins.

PATIENTS AND METHODS

Literature Search

We conducted a systematic search of the literature in PubMed (National Library of Medicine, Bethesda, MD) up to January 31, 2012, for cases of GBS-induced TSLS. We searched the MEDLINE database for the following terms: “group B streptococcus,” “*Streptococcus agalactiae*,” and “toxic shock syndrome.”

Case Reports

Case 1

A 61-year-old white woman with uncontrolled diabetes mellitus was admitted to Pikeville Medical Center in February 2011 with severe left leg pain 1 week after an inversion ankle sprain. The left leg was intensely tender with a 2 × 3-cm area of purplish skin discoloration. The patient had diffuse abdominal pain, nausea, several episodes of vomiting, and watery diarrhea and was initially managed with levofloxacin for possible invasive gastroenteritis. Two days later, the patient's condition deteriorated to septic shock and respiratory failure that required intubation and mechanical ventilation, intravenous fluids, vasopressors, and broad coverage antimicrobial therapy (meropenem, daptomycin, and linezolid). By that point, the patient had developed multiple areas of extensive skin erythema and hemorrhagic bullae over her left lower extremities. Laboratory values were white blood cell count (WBC) = 20,400 cells/μL (29% bands), platelets = 36,000 cells/μL, creatinine = 3.2 mg/dL, and total bilirubin levels = 3.1 mg/dL. Chest X-ray showed

diffuse infiltrates, and computed tomography (CT) imaging of the lower extremities revealed soft tissue swelling, but no evidence of fluid collection or necrotizing fasciitis. Two consecutive sets of blood cultures (each set consisting of aerobic and anaerobic bottles), drawn on admission before the initiation of antibiotic therapy, grew GBS in both the aerobic and anaerobic bottles. Gram staining of tissue specimens obtained during surgical debridement demonstrated gram-positive cocci in pairs and chains. Aerobic cultures of debrided tissues showed heavy pure growth of GBS, whereas anaerobic cultures were negative. The GBS isolated strain was resistant to erythromycin but susceptible to daptomycin, levofloxacin, linezolid, penicillin, vancomycin, and clindamycin. The GBS strain was tested for macrolide-lincosamide-streptogramin B (MLS_B) resistance; there was no blunting of the clindamycin inhibition zone proximal to the erythromycin disc suggestive of no inducible MLS_B resistance. Antimicrobial therapy was changed to the combination of clindamycin and ceftriaxone. Vaginal, throat, and rectal cultures were negative for GBS. The patient was extubated on day 5 and was transferred to the floor on hospital day 6. The leukocytosis, acute kidney injury, and liver dysfunction had completely resolved. Unfortunately, the patient died from acute respiratory failure secondary to mucous plug on day 8.

Case 2

A 65-year-old white woman with uncontrolled diabetes mellitus presented to Pikeville Medical Center in March 2011 with a 1-week history of severe pain of the left gluteal area. Two days later, the patient had purulent drainage from the gluteal area along with high-grade fever and chills. The left gluteal area was erythematous and intensely tender, with a necrotic open ulcer draining purulent brownish material. The patient was profoundly hypotensive (blood pressure, 65/40 mm Hg) and required support with oxygen, intravenous fluids, vasopressors, and antimicrobial agents (piperacillin/tazobactam, vancomycin, and linezolid). Laboratory values were WBC = 35,000 cells/ μ L (39% bands) and creatinine = 4.6 mg/dL. CT imaging of the pelvis revealed left gluteal necrotizing fasciitis. Emergent wide debridement was performed, and the intraoperative findings were typical for necrotizing fasciitis, including loss of tissue-plane resistance and necrosis of the subcutaneous fat. Gram-staining of samples and putrid drainage obtained during the operation demonstrated gram-positive cocci in pairs. Aerobic cultures of surgical specimens showed pure heavy growth of GBS, whereas anaerobic cultures were negative. We obtained pure cultures of GBS from 2 consecutive sets of blood cultures done before commencement of antibiotic treatment (both the aerobic and anaerobic bottles). The GBS strain was resistant to erythromycin but susceptible to daptomycin, levofloxacin, linezolid, penicillin, vancomycin, and clindamycin. The isolated GBS strain was tested for MLS_B resistance; there was no blunting of the clindamycin inhibition zone proximal to the erythromycin disc suggestive of no inducible MLS_B resistance. Vaginal and rectal cultures were positive for GBS. Antimicrobial therapy was changed to the combination of clindamycin and ceftriaxone. The leukocytosis and acute kidney injury had completely resolved. After 4 weeks of antimicrobial therapy, the outcome was favorable, and the patient was discharged home.

Bacterial Materials and Methods

Pyrogenic Toxin Production and Purification

The GBS strain isolated from the patient reported in Case 1 was cultured for 18 hours stationary in 1200 mL of pyrogen-free dialyzable beef-heart medium at 37°C in the presence of 7%

CO₂.⁵ Subsequently, the bacterial cells were removed by centrifugation (4000 \times g; 15 min), followed by filtration (0.2 μ m pore size). The resultant supernate was treated 2 hours with 4800 mL of 4°C absolute ethanol to precipitate pyrogenic toxins. The precipitate was resolubilized in pyrogen-free water at 100 \times concentrated relative to the original culture fluid concentration, and insoluble material was removed by centrifugation (14,000 \times g; 5 min).

Pyrogenic Toxin Assays

Streptococcus pyogenes bacteria (group A streptococci) are known for their production of pyrogenic toxins, notably SPEs. Pyrogenic toxins are now also recognized in group C and group G streptococci, and in many of these strains their pyrogenic toxins are related to those from group A streptococci.¹⁶ This raises the possibility that GBS produce known SPEs. Therefore, the 100 \times -concentrated GBS supernate from above was tested for SPEs A, B (cysteine protease), and C by reactivity against rabbit hyperimmune antisera raised in rabbits against individually purified SPEs.²⁴ The remaining concentrated supernate from the GBS strain was diluted in PBS (0.005 M sodium phosphate, pH 7.2; 0.15 M NaCl) until 10 \times -concentrated and unconcentrated relative to the original culture fluid. These solutions were tested for 2 defining properties of pyrogenic toxins, pyrogenicity in rabbits that typically peaks 4 hours postintravenous inoculation and ability to amplify the lethal effects of gram-negative LPS by up to 10⁶-fold.²⁴ Briefly, 3 Dutch-belted rabbits per group, either sex, were acclimated to a pyrogen test apparatus for 3 hours 1 day before use. The day of use the animals were re-acclimated to the apparatus for 1 hour with rectal thermometers inserted. The animals were injected with 1 mL/kg of the 10 \times -concentrated or unconcentrated GBS supernates. One group of animals was also injected with 1 μ g/kg of LPS from *Salmonella typhimurium* (1/500 lethal dose 50% endpoint).²³ Fever responses were recorded immediately before injection and hourly for a total of 4 hours. At the 4-hour time point, the rabbits treated with GBS supernates were given intravenous injections of 1 μ g/kg LPS and monitored for death over a 48-hour period. The animal studies were performed in accordance with an approved University of Minnesota IACUC protocol (0908A71722); as directed in this protocol, rabbits that could not right themselves and simultaneously could not exhibit escape behavior uniformly succumb, and these animals were thus prematurely euthanized with 1 mL/kg of Beuthansia D.

Statistical Methods

We used SAS software v. 9.1 (SAS, Inc., Cary, NC) to compare the pyrogenic characteristics of GBS supernates. Differences between fever responses in the groups of rabbits were determined using the Student t-test. P value of 0.05 was considered significant.

RESULTS

Pyrogenic Toxin Assays

The 100 \times -concentrated culture fluid from the GBS strain was negative when tested by antibody assay for SPEs A, B, and C. This was expected since we have not previously observed GBS to produce known group A streptococcal SPEs.^{15,28,29} As discussed above, 2 defining properties of pyrogenic toxins include the capacity to cause fever responses in rabbits that steadily rise and peak 4 hours postintravenous injection, and the ability to amplify the lethal effects of LPS.²² Fever responses in rabbits are considered significant when the average response of

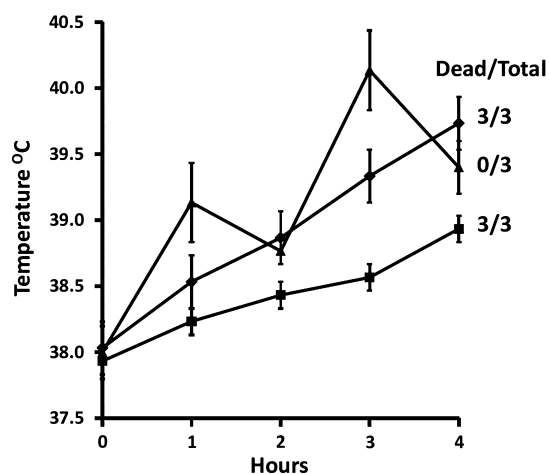


FIGURE 1. Pyrogenicity and capacity to enhance susceptibility to lethal LPS shock by supernates from *Streptococcus agalactiae*. Rabbits (3 per group) were injected intravenously with 1×-concentrated (solid square) or 10×-concentrated (solid diamond) *Streptococcus agalactiae* supernate, or 1 μg/kg LPS (solid pyramid). Fever responses were monitored for 4 hours. At the 4-hour time point, rabbits receiving GBS supernates were injected intravenously with 1 μg/kg LPS. Deaths due to enhancement of LPS shock were recorded as number of dead animals/total number of animals in each group over a 48-hour time period.

3 animals exceeds 0.5°C.²⁶ We therefore assayed 10×-concentrated and unconcentrated GBS culture fluid for these properties. Both 10×-concentrated and unconcentrated culture fluids were pyrogenic in rabbits, with fever peaks steadily rising for 4 hours postintravenous injection (Figure 1). The 10×-concentrated fluid caused an average fever response of 1.7°C at 4 hours ($p < 0.0004$ by the Student t test of unpaired data when 0 and 4 h temperatures were compared). Similarly, the unconcentrated culture fluid caused a 1.0°C average fever response at 4 hours postinjection ($p < 0.0005$ compared to 0 h temperatures). We cannot be certain that the GBS culture fluids would not cause fevers that rise beyond 4 hours since we were not approved by IACUC to extend measurements beyond 4 hours. However, the shape of the fever curves was typical of those expected with pyrogenic toxins. As a control for pyrogenicity, 3 rabbits also received 1 μg/kg of LPS intravenously. LPS typically causes fever responses in rabbits that peak at both 1 and 3 hours postinjection,²⁶ and this was seen in the rabbits injected with LPS (see Figure 1). All 3 rabbits in both groups that received the GBS culture fluids succumbed within 48 hours postinjection of 1 μg/kg of LPS intravenously, consistent with the properties of pyrogenic toxin superantigens. In contrast, none of the 3 rabbits treated with 1 μg/kg of LPS intravenously alone succumbed. Collectively, these data suggest that the GBS culture fluids contained pyrogenic toxins that induced fevers and amplified the lethal effects of LPS. Although we did not assess the extent of LPS amplification, the degree of increased susceptibility seen was at least 500-fold.

Literature Review

GBS-induced TSLS is rare; we identified only 11 documented cases in the literature.^{1,2,8,11,25,30,34,36,39,40} In the current study, we describe 2 new cases of GBS-induced TSLS. On reviewing the previously reported cases and our 2 new cases (Table 1), several comments can be made regarding clinical presentation and medical management. Malignancy (2/13;

15%), diabetes (3/13; 23%), and splenectomy (2/13; 15%) were the most likely underlying diseases. TSLS due to GBS initially presented as soft tissue pain in an extremity or the back in 9 patients (69%); an influenza-like syndrome characterized by fever, chills, myalgia, nausea, vomiting, and diarrhea in 8 patients (62%); and a change in the mental status in 4 patients (31%). Clinical signs of skin soft tissue infections consistent with localized swelling, erythema, and tenderness were observed in all patients, while ecchymoses, bulla formation, and sloughing of the skin were observed in 3 patients (25%). Scarletina-like erythema was observed in 3 patients (23%). Although initial laboratory studies may reveal only mild leukocytosis, the mean percentage of bands may reach 40%-50%. Eight of the 13 patients (62%) underwent surgical debridement and/or amputation of the affected areas. Antibiotics such as clindamycin that suppress protein synthesis and therefore toxin synthesis were not given (2 patients) or were delayed (not initiated until bacterial cultures returned positive) in 7 patients (54%). Eight of the 13 patients (62%) responded to medical and surgical management, while the rest died. Our results suggest again that GBS produces 1 or more related pyrogenic toxins. Concentrated culture fluids (100×) of the GBS failed to react with antisera to the 3 best-known SPEs. Thus, it is unlikely that the GBS strain made one of the known *Streptococcus pyogenes* SPEs; instead, it apparently produced a previously undescribed pyrogenic toxin.

DISCUSSION

Streptococcus agalactiae is emerging as a cause of fulminate illness similar to *Streptococcus pyogenes*-TSLS.^{1,2,8,11,23,28,32,34,36,37} Toxic shock syndrome is an acute, multisystem, toxin-mediated illness, typically resulting in shock and multiorgan failure. Bacterial pyrogenic toxins are central in the pathogenesis of TSS. These bacterial toxins trigger massive nonconventional T-cell activation, dependent only on the composition of the variable part of the β-chain of the T-cell receptor, with excessive cytokines from both T cells and antigen-presenting cells that cause tissue damage, disseminated intravascular disease, and organ dysfunction. The toxins have thus become referred to as superantigens.^{14,21,22} In the current study, we demonstrated that GBS produces uncharacterized pyrogenic toxin(s), explaining the ability of GBS to cause TSLS. We previously identified a novel pyrogenic toxin produced by GBS, which was isolated from a patient with TSLS, and showed that several GBS strains failed to make the known *Streptococcus pyogenes* SPEs, an observation consistent with the findings in the present study.^{26,28} The GBS strain from our patient produced a pyrogenic toxin that failed to cross-react immunologically with known SPEs, likely because the protein amino acid sequences differ significantly. Future studies are needed to characterize completely this pyrogenic toxin produced by GBS strains. Whether horizontal transfer of DNA-encoding pyrogenic toxins is occurring between different GBS strains, as has been shown for SPEs transferred by bacteriophages, remains to be proven.^{3,6} It is therefore plausible that such a mechanism is contributing to an increased incidence of severe invasive GBS diseases. Furthermore, GBS is capable of producing menstrual-related TSS in women with vaginal carriage of certain GBS strains. This phenomenon might be attributed to the ability of GBS pyrogenic toxins to cross vaginal mucosa.^{1,28}

Treatment of GBS-induced TSLS requires a multidisciplinary approach with immediate supportive measures, appropriate antimicrobial regimen, and surgical intervention. In women, vaginal examination should be performed, and any tampon or foreign body removed. As pyrogenic toxins are pivotal in TSLS, the addition of an agent with the ability to inhibit

TABLE 1. Group B Streptococcus Toxic Shock-Like Syndrome

Patient	Case Source First Author, Reference (Year)	Age (yr)/ Sex	Underlying Disease	Cause of TSLS	Treatment	Outcome
1	Thomas ⁴⁰ (1996)	51/F	Liver cirrhosis	Extensive cellulitis	Clindamycin	Survival
2	Gardam ¹¹ (1998)	67/F	CLL	Necrotizing fasciitis	Penicillin G, clindamycin, ceftriaxone, IVIG, left above the knee amputation and right calf debridement	Death
3	Crum ⁸ (2003)	43/M	DM, ESRD, necrotizing fasciitis of right lower extremity	Necrotizing fasciitis and myositis	Penicillin G, gentamicin, IVIG, debridement of left thigh	Survival
4	Schlievert ³⁰ (1993)	27/F	Healthy	Tampon	Ceftriaxone and clindamycin	Survival
5	Tang ³⁹ (2000)	75/F	Hypertension, PVD	Necrotizing fasciitis	Penicillin G, clindamycin, left above the knee amputation, open arthrotomy of right knee with irrigation	Death
6		64/M	Liver cirrhosis	Necrotizing fasciitis	Penicillin G, clindamycin, right above the knee amputation	Death
7	Reich ²⁵ (2004)	42/M	Splenectomy for ITP	Septic shock postsplenectomy	Cefazolin and clindamycin	Survival
8	Sims ³⁶ (2006)	42/M	Splenectomy for ITP	Septic shock postsplenectomy	Penicillin G and clindamycin	Survival
9	Bero ² (2006)	67/F	Metastatic melanoma	Skin abscess	Ceftriaxone, drainage of left thigh abscess	Survival
10	Begley ¹ (2007)	37/F	Healthy	Tampon	Vancomycin, cefazolin, clindamycin, and IVIG	Survival
11	Sendi ³⁴ (2009)	50/M	Healthy	Necrotizing fasciitis	Penicillin G and clindamycin	Survival
12 (Case 1)	PR	61/F	DM, morbid obesity, COPD, CAD	Extensive cellulitis	Ceftriaxone and clindamycin	Survival*
13 (Case 2)	PR	65/F	DM, morbid obesity, CAD	Necrotizing fasciitis	Ceftriaxone and clindamycin	Survival

Abbreviations: CAD = coronary artery disease, CLL = chronic lymphocytic leukemia, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, ESRD = end-stage renal disease, ITP = idiopathic thrombocytopenic purpura, IVIG = intravenous immunoglobulin, PR = present report, PVD = peripheral vascular disease.

*This patient initially survived but later died due to complications not related to TSLS.

bacterial protein syntheses is important to minimize the severity of this devastating disease. Protein synthesis inhibitors such as clindamycin and linezolid enhance the phagocytosis of *Streptococcus pyogenes* and do not exhibit reduced efficacy during the stationary phase of growth; their efficacy is not diminished due to bacterial load.^{7,12,13,35} Of additional concern is the potential for the loss of efficacy of erythromycin and clindamycin due to increasing rates of resistance expressed by GBS (32% and 15%, respectively).²⁴ The MLS_B phenotype is mediated by the erythromycin ribosomal methylation (erm) gene and has been previously identified in certain strains of *Streptococcus pyogenes* as well as other streptococcal species.^{18,19} Due to the importance of protein synthesis inhibition, it may be reasonable to consider linezolid as initial therapy until susceptibility to clindamycin is confirmed.

Conclusions

Any patient who presents with septic shock is a candidate for a prompt mucocutaneous examination and workup evaluation for TSS or TSLS. GBS produces uncharacterized pyrogenic toxins, explaining its ability to cause TSLS. For that reason, empiric antimicrobial therapy should include a protein synthesis inhibitor, preferably linezolid, while awaiting the results of susceptibility testing. Implementation of early, well-coordinated, and multidisciplinary approaches involving surgeons and infectious

disease and critical care specialists is required to prevent illness progression and death due to the aggressive form of invasive GBS infection.

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