

Group B Streptococcal Disease in Nonpregnant Adults

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Group B streptococcal (GBS) disease in nonpregnant adults is increasing, particularly in elderly persons and those with significant underlying diseases. Diabetes, neurological impairment, and cirrhosis increase risk for invasive GBS disease. Skin, soft-tissue, and osteoarticular infections, pneumonia, and urosepsis are common presentations. Meningitis and endocarditis are less common but associated with serious morbidity and mortality. Disease is frequently nosocomial and may be related to the placement of an iv catheter. Recurrent infection occurs in 4.3% of survivors. Capsular serotypes Ia, III, and V account for the majority of disease in nonpregnant adults. Although group B streptococci are susceptible to penicillin, minimum inhibitory concentrations are 4-fold to 8-fold higher than for group A streptococci. Resistance to erythromycin and clindamycin is increasing. The role of antibodies in protection against GBS disease in nonpregnant adults is unresolved. However, the immunogenicity of GBS vaccines being developed for prevention of neonatal disease should be assessed for adults who are at risk.

INCIDENCE AND EPIDEMIOLOGY

Despite the recent success of prevention efforts targeting neonatal group B streptococcal (GBS, *Streptococcus agalactiae*) disease [1], the rate of invasive GBS disease in adults continues to climb. Twofold to 4-fold increases in the incidence of invasive GBS infections in nonpregnant adults have been reported over the last 2 decades [2–5], with rates ranging from 4.1 to 7.2 cases per 100,000 nonpregnant adults. Given the decline in neonatal GBS disease, more than two-thirds of all invasive GBS disease in the United States now occurs in adults, most of which is unrelated to pregnancy. Disease rates increase with age and are twice as high in the black population as in the white population (table 1). The mean age of nonpregnant adults with invasive GBS disease is ~60 years, and the associated mortality rate is ~25%.

Although serious invasive GBS disease occurs in adults who are otherwise in good health, the majority of disease occurs in those with significant underlying conditions [3, 6]. Diabetes

mellitus is the most common comorbid condition, typically present in 20%–25% of nonpregnant adults with GBS disease. Last year in metropolitan Atlanta, >40% of younger adults (18–64 years old) with invasive GBS infection had diabetes. Other conditions, including cirrhosis, history of stroke, breast cancer, decubitus ulcer, and neurogenic bladder, have been associated with increased risk of invasive GBS disease in multivariate analysis [7]. Rates of GBS disease are 4 times higher among nursing facility residents than among individuals of the same age residing in the community [8], although the occurrence of secondary disease among nursing facility residents appears uncommon. Older patients hospitalized for GBS bacteremia are significantly more likely to be bedridden than are older patients who are hospitalized for other reasons [9].

The increasing rates of GBS disease may be attributed in part to an expanding population of adults who are living longer with significant medical conditions. It is interesting that the epidemiology may differ somewhat in developing countries, where overall life expectancy and survival rates for persons with chronic medical conditions are significantly less. In a recent review of 40 nonpregnant adults infected with invasive group B streptococci in Soweto, South Africa, the patients were younger than in developed countries (mean age, 45.6 years) and none had cancer or neurological disease, yet 25% had recent trauma associated with the onset of GBS infection [10].

A substantial proportion (17%–35%) of invasive GBS disease among nonpregnant adults occurs >2 days after admission to

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Table 1. Comparison of invasive group B streptococcal disease rates among adults in the Emerging Infections Program Network and in metropolitan Atlanta, 1998.

Age, years	Rate per 100,000 population			
	In ABCs, 1998 ^a	In Atlanta, 1998-1999, by racial group, % ^b		
		White	Black	Overall
18-34	2.1	0.7	5.4	2.5
35-49	3.4	1.7	7.5	3.4
50-64	8.7	6.7	20.8	10.4
>65	21.9	21.2	57.3	28.3

NOTE. Data include pregnant and nonpregnant adults. ABCs, Active Bacterial Core Surveillance of the Emerging Infections Program Network, Centers for Disease Control and Prevention.

^a Surveillance area includes California (3-county San Francisco Bay area); Connecticut; Georgia (20-county Atlanta area); Maryland; Minnesota (7-county Rochester area); Oregon (3-county Portland area); and Tennessee (5 urban counties). Surveillance area includes 22,392,985 persons. Based on data available at <http://www.cdc.gov/ncidod/dbmd/abc>.

^b Georgia Emerging Infections Program Surveillance (included in ABCs); 20-county Atlanta metropolitan statistical area (population, 3.7 million).

the hospital [3, 4, 7, 11]. Jackson et al. [7] noted that patients are hospitalized for a median of 4 days (range, 2-366 days) before cultures become positive for GBS. Nosocomial GBS disease may arise from new acquisition of the organism in the hospital or, perhaps more likely, from preexisting skin or mucosal colonization. The latter investigators found that individuals with nosocomial disease were 30 times more likely than uninfected, hospitalized control subjects to have had a central venous catheter placed prior to the onset of GBS disease [7]. Polymicrobial bacteremia, particularly coinfection with staphylococcal species, may be detected in >25% of GBS bacteremia episodes [3].

CLINICAL DISEASE

Clinical manifestations of GBS infection in adults are numerous and quite varied. Because group B streptococci may colonize skin and mucosal surfaces and may be isolated from infected sites along with other virulent organisms, their role in pathogenesis has often been questioned. However, studies of invasive GBS infection in which the organisms are isolated from normally sterile sites such as blood or CSF provide direct evidence that group B streptococci are the etiologic agents in many clinical syndromes. Table 2 lists common clinical diagnoses for adults with invasive GBS disease.

Skin and soft tissue infections. Skin and soft-tissue infections are the most frequently reported clinical syndromes associated with invasive group B streptococci. These infections most often present as cellulitis, decubitus ulcers, and infected foot ulcers. The latter occur exclusively in patients with diabetes

and are frequently complicated by osteomyelitis. Cellulitis occurs in individuals with predisposing local or regional conditions such as lymphatic or vascular insufficiency (including saphenous venectomy), radiation therapy, and chronic dermatitis (e.g., tinea pedis), or systemic conditions such as cirrhosis [3, 12, 13]. Patients with a history of breast cancer who have undergone mastectomy are susceptible to arm and chest wall cellulitis, in some instances many years after surgery [3, 7]. Several cases of breast cellulitis due to group B streptococci in patients who have undergone breast conservation therapy (lumpectomy, axillary node dissection, and postoperative radiation therapy) have been reported [14].

The presence of a decubitus ulcer has been associated with increased risk for invasive GBS disease in multivariate analysis [7]. Among 10 patients with infected decubitus ulcers who were identified in population-based surveillance for invasive GBS disease [3], 50% were nursing facility residents, 40% were paraplegic, 40% had dementia, and 33% had diabetes (unpublished data). Group B streptococci have occasionally been associated with wound and burn infections in nonpregnant adults. Cases of necrotizing fasciitis and toxic shock-like syndrome associated with group B streptococci have been reported rarely [15].

Bone and joint infections. GBS osteomyelitis most often occurs by contiguous spread or direct inoculation [16]. The bones of the foot are frequently involved; this involvement is linked with vascular insufficiency and overlying ulcers and spreads from adjacent skin and soft-tissue infection. Vertebral osteomyelitis, usually in the lumbosacral area, is another common form of GBS osteoarticular infection; hematogenous seed-

Table 2. Clinical diagnoses for adults with invasive group B streptococcal disease.

Skin, soft-tissue infection
Bacteremia with no identified focus
Pneumonia
Osteomyelitis
Bones of feet
Lumbosacral vertebrae
Urosepsis
Peritonitis
Septic arthritis
Monoarticular
Prosthetic joint infection
Meningitis
Endocarditis
IV catheter infection
Miscellaneous
Mycotic aneurysm
Pericarditis/myocarditis
Endophthalmitis

ing is the most likely mechanism of infection, and vertebral destruction is minimal. GBS septic arthritis is generally monoarticular, most often involving the knee, hip, or shoulder joints [16]. Late prosthetic joint infection with group B streptococci may result from bacteremic seeding during invasive procedures (e.g., sigmoidoscopy) or in the presence of a distant focus of infection (e.g., endocarditis). A history of bone surgery, implanted prosthetic hip joints, and diabetes mellitus were the most common conditions associated with GBS osteoarticular disease [16].

Pneumonia. GBS pneumonia generally occurs in older adults with neurological impairment resulting from conditions such as cerebrovascular disease or dementia. In many cases aspiration is either documented or suspected. Infiltrates can be unilobar or multilobar; pleural effusions are uncommon, and lung tissue necrosis is rare.

Urosepsis. Between 5% and 23% of nonpregnant adults with invasive GBS disease present with a urinary tract infection [2, 3, 5, 7, 9, 15, 17]. It is more common in older individuals (mean age, 71 years). Trivalle et al. [9] found that urinary tract infection was the clinical diagnosis for 39% of nonpregnant adults >70 years of age with GBS bacteremia, compared with only 6% of patients 15–70 years of age. Many patients with GBS urosepsis (more than one-third in our series [3]) are nursing facility residents. Most patients have significant predisposing conditions, such as diabetes mellitus, prostate disease, a prior history of urinary tract infections, an indwelling urinary catheter, and anatomic abnormalities of the urinary tract [11, 17–19]. The presence of a neurogenic bladder has been associated with significantly increased risk for invasive GBS disease, in comparison with the risk for hospitalized control subjects [7].

Meningitis. GBS meningitis is an important but uncommon manifestation of invasive GBS disease in adults [3], and it may account for up to 4% of all cases of bacterial meningitis in adults [20]. Most cases occur in postpartum women, elderly adults, or adults with significant underlying diseases. Symptoms are generally abrupt in onset, and bacteremia is present in ~80% of cases [20, 21]. A distant focus of infection, such as the endometrium or endocarditis, is frequently identified. The case-fatality rate is high (27%–34%) and closely linked with the presence of underlying conditions other than pregnancy. A small but significant proportion of survivors (7%) are left with permanent hearing loss.

Endocarditis. GBS endocarditis accounts for 2%–18% of invasive disease in adults [3, 18, 22, 23]. Early reports of GBS endocarditis focused on acute disease in parturient women, many of whom had rheumatic heart disease. Although postpartum GBS endocarditis still occurs (I am aware of 2 local cases requiring surgery that occurred in the past year), we now know that both acute and subacute endocarditis can occur in

nonpregnant adults (mean age, ~50 years) with or without known valvular disease. The vegetations can be quite large and friable (figure 1), and large-vessel embolization is common [24, 25]. Infection may be further complicated by pericarditis, myocarditis, endophthalmitis, and mycotic aneurysms.

Several recent reports suggest that GBS endocarditis may be underrecognized. Simon and Smith [26] reviewed GBS bacteremia in 50 nonpregnant adults and found that of 12 patients who underwent echocardiography, 7 had vegetations (58% of those studied by echocardiography and 14% overall of those with bacteremia). Harrison et al. [27] found that endocarditis was present in over a quarter of adult patients who had a recurrent episode of invasive GBS disease a median of 10 weeks after the initial episode. Mortality approaching 50% was noted in older reports [28]. However, a case-fatality rate of 13% was noted recently among a select group of aggressively treated patients (48% underwent cardiac surgery) with β -hemolytic streptococcal endocarditis, more than half of whom had GBS infection (25).

Intravascular catheters. Group B streptococci have been associated with infection of iv catheters, arterial lines, polytetrafluoroethylene grafts, and an iv pacemaker wire. Coinfection with *Staphylococcus aureus* is common in patients who have GBS infection that is associated with the presence of an intravascular device [3, 11].

Recurrent invasive GBS infection. Recurrent episodes of invasive infection due to group B streptococci may occur in as many as 4.3% of patients who survive the initial episode of disease [27]. Most are cases of relapsing disease, as determined

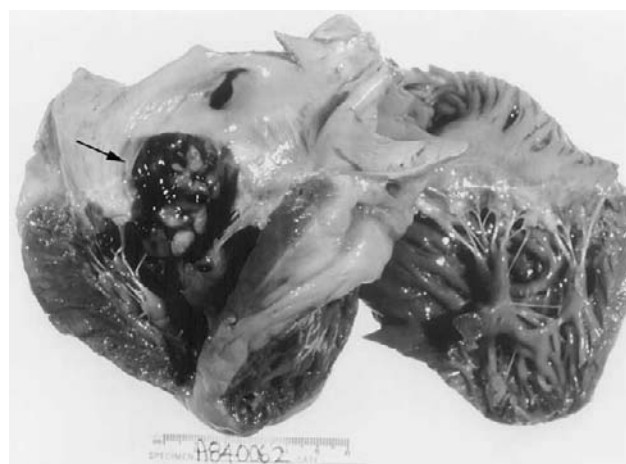


Figure 1. Group B streptococcal endocarditis. Gross pathology, at autopsy, of the heart of a 63-year-old man with longstanding diabetes and morbid obesity who died of invasive group B streptococcal disease. The arrow indicates the large vegetation overlying the mitral valve. Additional autopsy findings included evidence of purulent meningitis, septic embolism in the dorsalis pedis artery, and focal infarcts in the spleen (not shown).

by molecular footprinting of the isolates, and in such cases the interval between episodes is shorter (mean of 14 weeks, vs. 43 weeks when infection is with a different strain). In more than one-third of recurrences, the patients presented with deep-seated infections such as endocarditis or osteomyelitis that were not present (or at least not recognized) during the first episode of GBS infection. Since penicillin treatment of GBS infection does not eradicate carriage of group B streptococci, relapse may also be attributed to re-infection with group B streptococci colonizing the skin or gastrointestinal or genital surfaces. Although all episodes of GBS bacteremia should prompt a search for the focus of disease, patients who have recurrent episodes must be thoroughly evaluated for a deep site of infection, and the evaluation should routinely include echocardiography.

MICROBIOLOGY AND DIAGNOSIS

On sheep's blood agar, group B streptococci form smooth white colonies, usually surrounded by a zone of hemolysis that is narrower and less definite than those of group A, C, or G streptococci. Serological typing based upon detection of the group-specific cell wall antigen provides definitive diagnosis. Selective media containing antibiotics are recommended for optimal detection of low levels of GBS colonization of the genital and gastrointestinal tracts [6].

Group B streptococci can be subtyped into at least 10 capsular polysaccharide serotypes; types Ia, Ib/c, Ia/c, II, III, and V are most common in the United States. The presence of sufficient IgG antibody to the group B streptococci serotype-specific capsular polysaccharide protects against systemic infection in neonates [28]. The serotype distribution of isolates causing both neonatal and adult disease has shifted in the past decade. The earlier dominance of serotype III in early and late-onset neonatal disease has given way to a more balanced distribution between serotype Ia (35%–40%), type III (30%), and type V (15%–20%) in early onset neonatal GBS disease [28]. Types Ia, III, and V are also currently the most common serotypes in adult disease, in nearly equal proportions (table 3). Minor geographic variations in serotype distribution have been noted in the United States and Canada [15, 28], but more significant differences have been reported from Japan [28]. The serotype distribution appears to be continuously evolving, making ongoing surveillance essential to vaccine-development efforts (see Prevention section below).

TREATMENT

Group B streptococci remain susceptible to penicillin G, ampicillin, and other semisynthetic penicillins, although the MIC of penicillin is frequently 4-fold to 8-fold higher for group B streptococci than for group A streptococci (mean, 0.045 μ g/

Table 3. Serotype distribution of group B streptococcal isolates from pregnant and nonpregnant adults with invasive disease in Atlanta.

Serotype	Adults with isolate, %			
	Pregnant		Not pregnant	
	1992–1993 ^a (n = 32)	1998–1999 ^b (n = 17)	1992–1993 ^a (n = 65)	1998–1999 ^b (n = 196)
Ia/Ia/c	41	35	31	23
Ib/c	12	0	6	13
II	3	24	8	13
III	19	35	21	19
IV	0	0	0	0.5
V	25	0	31	24
VI	0	0	0	0
VII	0	0	0	0
Not typeable	0	6	3	8

^a Data from Blumberg et al. [4].

^b Isolates collected in metropolitan Atlanta as part of Active Bacterial Core Surveillance, which is a component of the Georgia Emerging Infections Program.

mL vs. 0.009 μ g/mL) [18, 29]. Resistance to clindamycin and erythromycin is increasing and may be present in as many as 15%–20% of group B streptococci isolates [30, 31]. Erythromycin and clindamycin resistance varies by geographic region of the United States and may be higher among serotype V isolates [31]. Vancomycin, chloramphenicol, first- and second-generation cephalosporins (excluding cefoxitin), and third-generation cephalosporins are effective alternatives. Aminoglycosides have little to no activity against group B streptococci when used alone but provide synergistic activity when combined with ampicillin or penicillin G [29]. Penicillin tolerance has been reported with regard to a small subset of group B streptococci isolates, and although it is of questionable clinical relevance, MIC/MBC testing may be considered in refractory cases.

Given the somewhat higher MICs, higher doses of penicillin G are recommended for treatment of serious GBS infections, particularly meningitis. The optimal duration of antibiotic treatment against invasive group B streptococci in adults has not been established, but a minimum of 2 weeks of therapy should be considered. Longer courses (lasting at least 4 weeks) are necessary for endocarditis and osteomyelitis and may be considered for episodes of recurrent invasive GBS disease, regardless of the focus identified. The addition of gentamicin can be empirically considered for fulminant disease and deep-seated infections such as endocarditis. With the rapid emergence of penicillin resistance among pneumococcal isolates and the significant recent increase in the use of penicillin to prevent neonatal GBS disease, the antibiotic susceptibility patterns of GBS isolates must be closely monitored.

Surgical management may be required for successful treat-

ment of GBS disease, particularly soft-tissue and bone disease. Abscess drainage and debridement of devitalized tissue are essential when loculated fluid or necrosis is present. Amputation may be necessary for successful treatment of foot infections in patients who have diabetes and peripheral neuropathy and vascular disease and who fail to respond to conservative management. Open arthrotomy and removal of prosthetic joint implants may be required in some cases of GBS septic arthritis. In some cases, GBS endocarditis can cause destruction of a valve or major embolic complications that necessitate early valve replacement [24, 25].

PREVENTION

General. Meticulous attention to skin care may prevent more-serious invasive GBS disease, particularly in patients who are elderly, bedridden, and/or have diabetes. Patients who have diabetes should be educated about proper foot care, and foot ulcers should be promptly treated to prevent local extension or systemic disease. Measures should be taken to avoid chronic pressure points and reduce the risk of decubitus ulcer formation in patients who are wheelchair-bound or bedridden. Chronic dermatologic conditions, including tinea pedis, should be treated aggressively.

Vaccines. Multivalent polysaccharide-protein conjugate vaccines based on serotype-specific capsular polysaccharides are in development for prevention of neonatal GBS disease. Although groups of adults at high risk for invasive GBS disease have been identified, the role of capsular polysaccharide antibodies in the prevention of either localized or invasive GBS disease in nonpregnant adults has not been adequately evaluated. Older adults and those with significant underlying diseases may have other defects (e.g., phagocyte or complement dysfunction or impaired macrophage Fc γ -receptor function) that contribute to an increased risk of GBS infection.

Wessels et al. [32] found substantial levels (≥ 3.5 $\mu\text{g/mL}$) of IgG antibodies to the infecting strain in acute serum from 7 of 12 nonpregnant adults with invasive GBS disease. Antibody levels were surprisingly high in these adults, and opsonic activity was normal in most cases. Although the results suggest that the presence of a sufficient level of opsonic antibody was not protective against invasive group B streptococci in these 7 patients, it is possible that the antibody levels measured at the time of admission had already risen in response to subclinical infection that was present before hospitalization. Antibody levels were relatively low in the remaining 5 patients, including the only 2 who died.

Many questions remain, and additional work is needed to expand the serological findings and define other immune defects that predispose to GBS disease in adults. The immediate priority for vaccine development is appropriately focused on

prevention of neonatal disease [33]. Capsule serotypes associated with neonatal disease (including Ia, III, and V) being evaluated for inclusion in multivalent conjugate vaccines also account for a large proportion of serotypes associated with adult disease. Since vaccine-induced antibodies *may* be protective in nonpregnant adults, future assessment of the immunogenicity of GBS conjugate vaccines in adults at risk is important.

CONCLUSION

GBS infections are a growing problem in older adults and those with chronic medical conditions, particularly diabetes mellitus. Skin and soft-tissue infection, bacteremia without an identified focus, pneumonia, urosepsis, and osteoarticular disease are among the most common clinical presentations. Endocarditis and meningitis are less common but very serious disease manifestations. The groups of adults at greatest risk have been carefully defined. Early recognition of infection, a search for deep-seated infection, appropriate antimicrobial therapy, and in some cases concomitant surgical intervention are essential elements of successful management of GBS disease.

The aging of the United States population and the substantial progress with treatment of chronic medical conditions provide an expanding number of patients at risk for invasive group B streptococci. Increasing rates of GBS disease among adults may be an unanticipated consequence of technological advances in modern medicine. If rates of disease continue to climb, prevention efforts for adults will take on greater priority.

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