

High Morbidity Associated with Invasive Group B Streptococcal Disease among Nonpregnant Adults in Thailand, 1999 to 2009

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ABSTRACT

Objectives: We aimed to describe clinical characteristics including outcomes among nonpregnant adults with invasive group B streptococcal (GBS).

Methods: A retrospective cohort study was conducted in patients with positive culture results for *Streptococcus agalactiae* during 1999-2009. Factors associated with surgical procedures were determined.

Results: A total of 101 patients with invasive GBS disease were identified. A mean (SD) age was 60.1 (16.1) years and 60 (59.4%) were females. Of 79 (78.2%) patients who had underlying condition, the most frequent was diabetes mellitus (34.6%). Common clinical syndromes were bone and joint infection (37.6%), skin and soft tissue infection (16.8%), and intra-abdominal infection (12.9%). Median (IQR) duration of hospitalization was 16 (9-24) days. Overall, 25 (24.8%) patients had at least one medical complication (e.g. shock or acute renal failure) and 36 (35.6%) patients experienced some surgical procedures. By multiple logistic regression, underlying disease (OR, 0.13; 95% CI, 0.02-0.66, $p = 0.014$), focal infection (OR, 19.4; 95% CI, 4.47-89.08, $p < 0.001$), positive joint fluid culture (OR, 75.73; 95% CI, 7.19-797.39, $p < 0.001$), and medical complication (OR, 9.07; 95% CI, 2.01-40.84, $p = 0.004$) were associated with the surgical procedure. The crude mortality was 8.9%.

Conclusion: Even low mortality in nonpregnant adults with invasive GBS disease was found, high morbidity including surgical procedure was determined. (*J Infect Dis Antimicrob Agents* 2011;28:169-77.)

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INTRODUCTION

Group B streptococci (GBS; *Streptococcus agalactiae*) is a beta-hemolytic gram-positive microorganism, which has been recognized as a cause of infection in pregnant women and newborn infants.¹ There is a substantial decline in the incidence of GBS infection in newborns due to prevention by use of prophylactic intrapartum antibiotics.² However, GBS has been considered as an unusual pathogen in nonpregnant adults, and the rate of invasive GBS disease in adults continues to climb.³⁻⁶ Clinical manifestations of GBS infection in adults are numerous, quite varied and range from focal to systemic infections, such as urinary tract infection,^{7,8} skin and soft tissue infections including necrotizing fasciitis,^{9,10} bone and joint infections,¹¹⁻¹³ pneumonia,^{6,14} meningitis,¹⁵ endocarditis,¹⁶ and primary bacteremia.^{6,10,17} High prevalence of underlying medical conditions among infected adults has been documented,^{6,8,10,17-19} such as diabetes mellitus^{6,9,17,18} and malignancies.^{4,17,18}

Several case reports and recent studies have suggested that such infections cause substantial morbidity and mortality. The reported mortality rate ranged from 9.3-32%.^{4,9,17,18,20,21} High mortality may be related to some factors, such as shock at diagnosis,^{4,18,20} bacteremia,⁹ thrombocytopenia,⁴ serotype,¹⁰ malignancy,¹⁸ and consciousness impairment.²⁰ Although a high morbidity has been observed in clinical practice, studies addressing this issue are limited.

The knowledge of epidemiology, clinical characteristics, and treatment outcome associated with invasive GBS infection in different geographical settings are essential for the implementation of effective prevention and treatment strategies. Almost all studies of GBS infection in nonpregnant adults have originated in the industrial world and little

information is available in the English-language literature regarding GBS infection occurring in Asia.¹⁷ We report a large series of nonpregnant adults with GBS infection in the state of clinical manifestation, associated conditions, and clinical outcomes in Thailand. We also address the issue of high morbidity associated with this condition.

PATIENTS AND METHODS

A retrospective study was conducted at Ramathibodi Hospital (a 1,000-bed university hospital of the Mahidol University, Bangkok, Thailand). Patients with invasive GBS infection were identified from the medical records and clinical microbiology laboratory records between January 1999 and December 2009. Their demographic, clinical presentations, including antimicrobial susceptibility, and clinical outcomes were reviewed. The study was reviewed and approved by the institute review board.

Invasive infections were diagnosed on the basis of the isolation of GBS from normal sterile sites, that were blood, joint fluid, pleural fluid, cerebrospinal fluid (CSF), pericardial fluid, operative samples of pus or tissue, and pus or tissue obtained from a site of focal suppuration at surgery. Patients with urinary tract infection were not included unless they had bacteremia. Nosocomial infection was defined as GBS infection occurring more than 48 hours after hospital admission when there had been no evidence of GBS infection at the time of admission.

Bacteremia was defined as isolation of GBS from one or more blood culture(s). If primary site of active infection could not be established and GBS was recovered only from blood, the episode was classified as primary bacteremia. Bacteremia with a focal site of infection was determined on the basis of bacteremia and clinical data and/or by a culture of tissue and/or fluid of another site

that was positive for GBS. Focal infection was only defined as clinical data and/or by a positive culture of tissue and/or fluid for GBS without bacteremia.

Blood samples were processed using the Bactec® system (Becton Dickinson) or BacT/Alert® System (Organon Teknika). Other specimens that are normally devoid of indigenous flora were plated on blood and chocolate agar plates and incubated overnight at 35-37°C. GBS was identified by gram staining, culture morphology, beta-hemolysis of sheep blood agar, positive CAMP test, resistance to bacitracin, negative bile-esculin test, and 6.5% NaCl tolerance test. Susceptibility tests were performed by disk diffusion method as recommended by the Clinical and Laboratory Standards Institute (CLSI).

Statistical analysis

Chi-square test or Fisher's exact test and Student's t-test were used to compare categorical variables and continuous variables between the two groups, respectively. Logistic regression was used to determine the factors associated with the outcome of GBS infection which was surgical procedure. The odds ratio (OR) and its 95% confidence interval (CI) were estimated. A p-value <0.05 was considered statistically significant. Variables that presented $p < 0.10$, were considered in a multivariate logistic regression model after assessment of multicollinearity of variance inflation factors. Variables were selected out from a multiple logistic regression model with backward stepwise selection and ones that attained a level of significance ($p < 0.05$) were retained in the model. All statistical analyses were performed using Stata statistical software version 10.0 (Stata Statistical Software: Release 10.0, Stata Corporation, College Station, TX, 2007).

RESULTS

During the 11-year study period, 169 patients with invasive GBS infections were identified from the database. Of these, 5 patients were pregnant women, 2 patients were diagnosed from autopsy, 31 patients were children, and medical charts of 30 patients could not be retrieved and reviewed. A total of 101 patients of invasive GBS infections were included in the analysis. The demographic data and clinical presentation are summarized in Table 1. Mean (standard deviation; SD) age was 60.1 (16.1) and age ranged from 15.3 to 91.6 years. Of these, 60 (59.4%) were females and 79 (78.2%) had at least one of the following underlying conditions, which were diabetes mellitus (34.6%), followed by hypertension (34.6%), and cardiovascular diseases (24.8%). Ninety-four patients (93.1%) had community-acquired infections. Of 121 positive culture specimens, the most common specimens were blood 58.7%, joint fluid 17.4%, and pus 8.3%. The most common clinical syndrome was bacteremia (71 patients, 70.3%). Of these, 47 (46.5%) patients had bacteremia associated with a focal infection, while 24 (23.8%) patients had primary bacteremia. Thirty (29.7%) patients had focal infection only. The most frequent sites of infection were bone and joint (37.6%), skin and soft tissue (16.8%), and intra-abdomen (12.9%).

Patients were hospitalized in 82 (81.2%) cases, treated in out-patient setting in 13 (12.9%) cases, and referred to another hospital in 6 (5.9%) cases. The specimen isolates were susceptible to penicillin (98%), erythromycin (99%), and cephalothin (100%). Most of the patients were treated with β -lactam antimicrobial agents such as penicillin or cephalosporin alone.

Median (IQR) duration of hospitalization was 16 (9-24) days; however, it ranged from 1 to 218 days. Four patients were lost to follow up and the outcome could not be established. Of the remaining

Table 1. Characteristics of 101 non-pregnant adults with invasive Streptococcal group B disease.

Characteristics	N=101
Mean (SD) age, years	60.1 (16.1)
Gender, n (%)	
Male	41 (40.6)
Female	60 (59.4)
Underlying condition, n (%)*	79 (78.2)
Diabetes mellitus	35 (34.6)
Hypertension	35 (34.6)
Cardiovascular disease	24 (24.8)
Solid malignancy	22 (21.8)
Chronic kidney disease	14 (13.9)
Orthopedics or rheumatic disease	14 (13.9)
Cirrhosis and other liver disease	11 (10.9)
Neurologic disorder	7 (6.9)
Prednisolone and chemotherapy	6 (5.9)
Hematologic malignancy	2 (2.0)
HIV/AIDS	2 (2.0)
Urinary catheter	2 (2.0)
Other renal disease	1 (1.0)
Other	16 (15.8)
Positive culture specimens, n (%)**	
Blood	71 (58.7)
Joint fluid	21 (17.4)
Pus	10 (8.3)
Tissue	6 (5.0)
Cerebrospinal fluid	3 (2.5)
Urine	2 (1.6)
Other***	8 (6.6)
Focal site of infection, n (%)	
Bone and joint	38 (37.6)
Skin and soft tissue	17 (16.8)
Intra-abdomen	13 (12.9)
Central nervous system	10 (9.9)
Pneumonia and/or empyema	4 (4.0)
Endocarditis	3 (3.0)
Gynecology system	2 (2.0)
Genitourinary tract	2 (2.0)
Endophthalmitis	1 (1.0)
Other	3 (3.0)

Abbreviation: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; SD, standard deviation

*some patients might have more than one underlying disease.

**some patient might have more than one positive culture specimen. Denominator was 121.

***ascitic fluid, peritoneal dialysate, bile, pleural fluid, bronchoalveolar lavage fluid, and sputum

97 patients, the overall mortality rate was 8.9%, while GBS related mortality rate was 7.9%. Common medical complications following invasive GBS infection were found in 25 (24.8%) patients, including acute renal failure (16 patients), intensive care unit admission (8 patients), shock (6 patients), severe metabolic acidosis (4 patients), and acute myocardial infarction (3 patients). Disseminated intravascular coagulopathy, septic emboli, and chronic multifocal abscess were found in one case each.

Overall, 36 (35.6%) patients experienced some surgical procedures. The most common surgical procedure was orthopedic surgery, especially opened arthrotomy for septic arthritis in 23 (22.8%) patients. Other surgical procedures such as explored laparotomy with or without other procedure (6 patients), debridement of localized soft tissue or bone infection (5 patient), incision and drainage (2 patients), dissectomy (1 patient),

enucleation (1 patient), and lobectomy left thyroid (1 patient) were also performed. Five patients underwent more than one surgical procedure and all were associated with septic arthritis. Number of total patients with invasive GBS disease and number of patients who experienced some surgical procedure stratified by year are demonstrated in Figure 1. By Kaplan-Meier analysis, median time to surgery was 2 days (Figure 2).

Clinical characteristics of patients stratified by undergoing surgical procedure status are shown in Table 2. Patients who experienced surgical procedure had lower proportion of underlying disease (64.9% vs. 88.1%), positive blood culture (42.9% vs. 89.8%), in contrast, higher proportion of positive joint fluid culture (47.6% vs. 1.7%), focal infection only (57.1% vs. 10.1%), and medical complication (35.7% vs. 17.0%) ($p < 0.05$, all). By multiple logistic regression, underlying disease (OR, 0.13; 95% CI, 0.02-0.66,

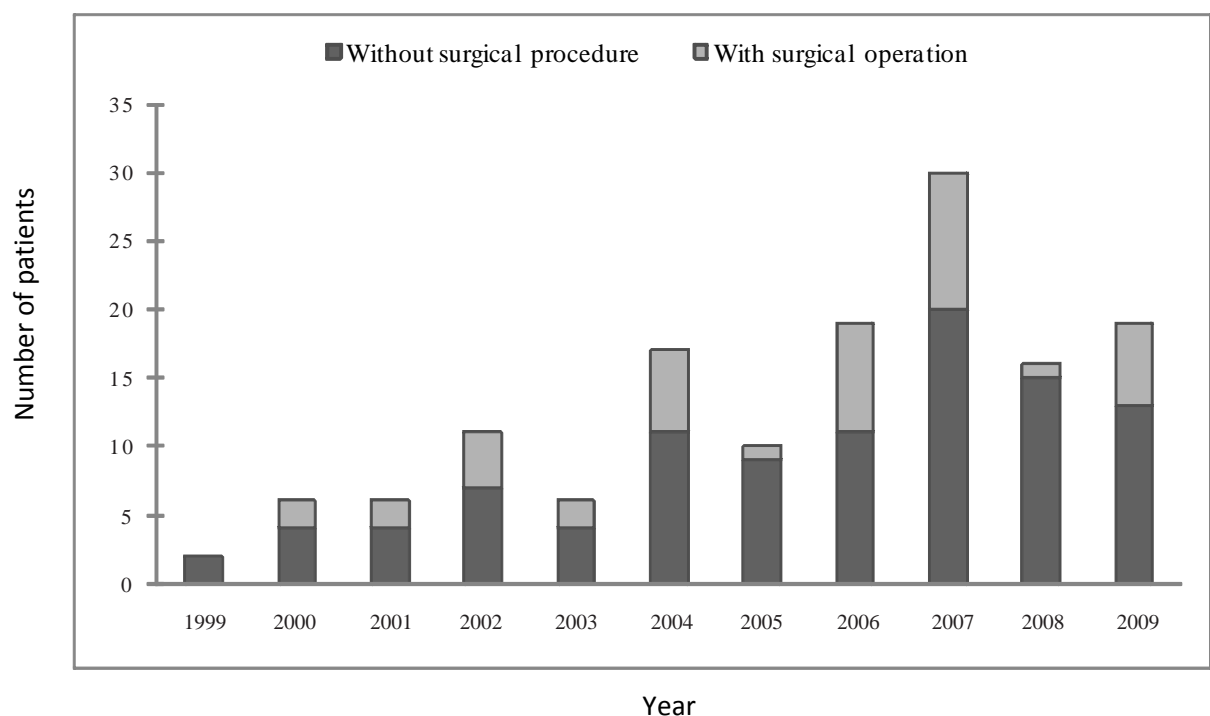


Figure 1. Number of cases with invasive streptococcal group B disease and number of patients whom underwent surgical procedure stratified by year.

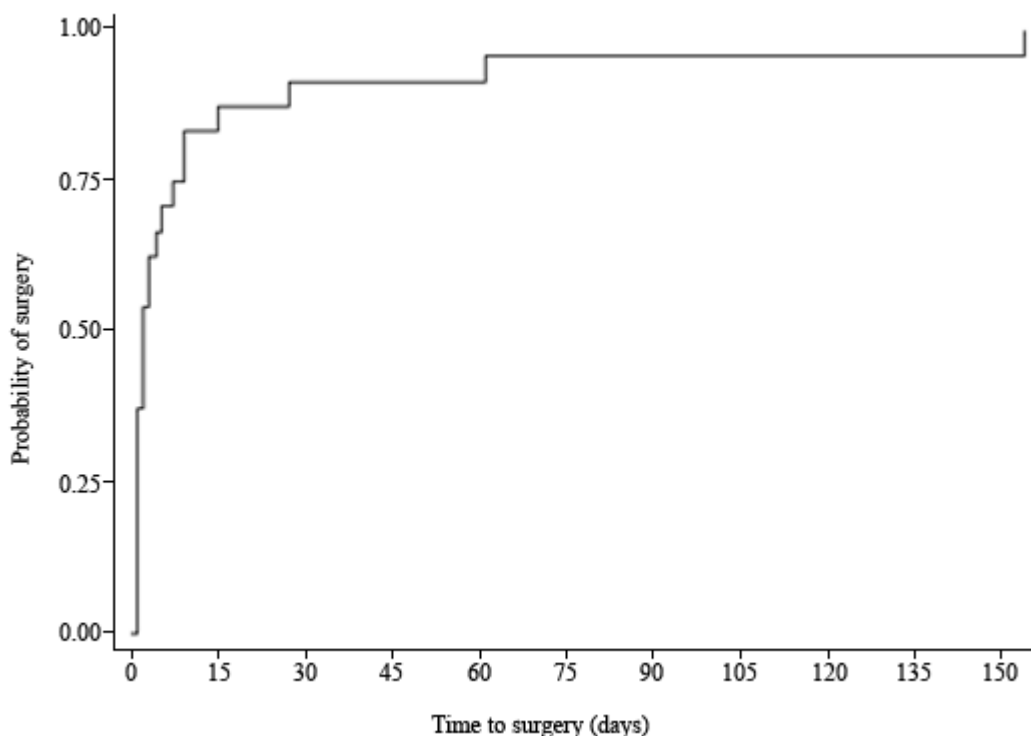


Figure 2. Kaplan-Meier analysis for median time to undergo surgical procedure among 101 nonpregnant adults with invasive group B streptococcal disease.

Table 2. Characteristics of 101 nonpregnant adults stratified by underwent surgical procedure outcome.

Characteristics	Surgical procedure		P-value
	No (N=59)	Yes (N=42)	
Mean (SD) age, years	59.1 (17.4)	61.4 (14.2)	0.504
Male gender, n (%)	34 (57.6)	26 (61.9)	0.687
Had underlying condition, n (%)	52 (88.1)	27 (64.9)	0.007
Type of infection, n (%)			1.000
Community-acquired infection	55 (93.2)	32 (92.9)	
Nosocomial infection	4 (6.8)	3 (7.1)	
Positive blood culture, n (%)	53 (89.8)	18 (42.9)	<0.001
Positive joint fluid culture, n (%)	1 (1.7)	20 (47.6)	<0.001
Focal infection only, n (%)	6 (10.1)	24 (57.1)	<0.001
Median (IQR) total duration of hospitalization, n (%)	14 (7-19)	18 (10-30)	0.159
Had complication, n (%)	10 (17)	15 (35.7)	0.037

Abbreviation: IQR, interquartile range; SD, standard deviation

$p=0.014$), focal infection (OR, 19.4; 95% CI, 4.47-89.08, $p < 0.001$), positive culture of joint fluid (OR, 75.73; 95% CI, 7.19-797.39, $p < 0.001$), and medical complication (OR, 9.07; 95% CI, 2.01-40.84, $p=0.004$) were associated with surgical procedure. The crude mortality was 8.9%. There was no statistically significant difference in mortality between patients who experienced surgical procedure and those who did not (10.3% vs. 8.6%, $p=1.000$).

DISCUSSION

To our knowledge, this is one of the largest reported series of nonpregnant adults with invasive GBS disease in Southeast Asia, especially in Thailand. The actual incidence of GBS infections among Thai adults is unknown because no population-based study has been previously performed. The average age of our patients was 60 years as reported in other series,^{4,5,17,18,20} in contrast to the recent study in Thailand that reported younger patients with GBS infection.¹⁷ Most patients had underlying conditions, however, approximately 20% had no underlying conditions. Even low mortality was found in this study, and high morbidity was determined.

The distribution of underlying diseases in patients with invasive GBS has varied in different studies. We found a high rate of underlying conditions in the adult patients with invasive GBS disease, probably related to increases in the prevalence of underlying medical conditions such as diabetes in older adults³⁻⁵ or longer survival of the patients with underlying conditions predisposed to this infection.¹⁹ Diabetes mellitus and malignancy are common co-morbid conditions in the present study which were comparable with the previous studies.^{3,4,17,19,21} Although human immunodeficiency virus (HIV) infected patients have a risk for invasive GBS infection over 30 times that seen in persons without HIV infection,²² only two HIV-infected

patients were identified, and one patient also had breast cancer. It is unknown why patients have a higher susceptibility to infection with GBS, but it has been suggested that impairment of phagocytosis and intracellular killing by neutrophil may be a predisposition to bacterial infection.^{23,24}

A variety of invasive GBS infections have been reported. The clinical spectrum of the disease ranges from mild soft tissue infections to severe bacteremia coupled with septic shock. Most studies of GBS disease in nonpregnant adults have reported skin and soft tissue infection and primary bacteremia as the leading clinical manifestation.^{3-5,17,18,22} In our study, bacteremia associated focal infection followed by bone and joint infections were the most common clinical manifestations.

The high rate (98%) of isolates susceptible to penicillin in this study confirms that it remains the drug of choice for invasive GBS. Although GBS is still susceptible to many antimicrobial agents, the morbidity and mortality are high.

The reported mortality rate attributed directly to GBS infection ranged from 9.3-25.5%,^{4,6,17,18,20} which was unlike our finding of rather low mortality rate. In contrast, we demonstrated high morbidity which was either complications or experienced surgical procedures in a substantial number of patients. Most of them were diagnosed as septic arthritis and underwent open arthrotomy. This is the first few studies which determined factors associated with undergoing any surgical procedure requirement. Patients with focal infection, had positive joint fluid culture, and had medical complications had higher odds of surgical procedure. This information may be helpful for physicians to predict clinical outcome and arrange the treatment plan which could minimize morbidity and mortality.

There were limitations to our study. First, clinical information collected from medical charts was not

complete due to destroyed medical charts. Second, risk factor for invasive GBS disease could not be evaluated directly due to there being no control group. Last, we did not perform serotype which might be associated with the severity of the disease.

In conclusion, invasive GBS disease in nonpregnant adults is not uncommon and we determined a wide range of clinical presentations. It causes serious diseases in nonpregnant adults, especially in the elderly and in patients with chronic underlying conditions. Even though low mortality was found, high morbidity including undergoing surgical procedure was determined. Early recognition of GBS infection, search for foci of infection, appropriate antimicrobial therapy, and concomitant surgical intervention in some cases, are essential for successful management of invasive GBS disease.

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