Original Article

# Prevalence, Predictors, Echocardiographic Features, and Clinical Outcomes of Infective Endocarditis in Patients with *Streptococcus agalactiae* Septicemia

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**Background**: *Streptococcus agalactiae* or Group B *Streptococcus* (GBS) infective endocarditis (IE) is less common but associated with serious morbidity and mortality. Evidence regarding the prevalence of GBS IE in patients with GBS septicemia is scant. There is also no recommendation for the use of echocardiography in patients with GBS septicemia in the current guidelines.

**Objective**: The primary objective was to determine the prevalence of GBS IE in patients with GBS septicemia. The secondary objective was to assess the predictors, echocardiographic features, and clinical outcomes, including in-hospital mortality, and valvular surgery in patients with GBS IE.

**Materials and Methods**: Consecutive patients older than 18 admitted to Siriraj Hospital due to GBS septicemia between 2005 and 2019 were enrolled. The patients' characteristics, echocardiographic index reports, and clinical outcomes were reviewed. Univariable and multivariable analyses were performed to determine the predictors of GBS IE. Clinical outcomes of patients with and without GBS IE were compared. A p-value of less than 0.05 was considered statistically significant.

**Results**: Two hundred seven patients were included in the present study. The prevalence of GBS IE was 10.6% (95% CI 6.8 to 15.6). Age, new murmur, and stroke/systemic embolism (SE) were independent predictors for IE in the patients with GBS septicemia. GBS IE caused a sizable proportion of intracardiac complications (36.4%) and moderate-severe valvular regurgitation (68.2%). There was a significant higher rate of in-hospital mortality and valvular surgery in the IE group than in the non-IE group at 63.3% versus 14.1% (p<0.001).

**Conclusion**: There was a sizable proportion of GBS IE in patients admitted due to GBS septicemia. Younger age, new murmur, and stroke/SE were independent predictors of IE in patients with GBS septicemia. Echocardiography should be performed in patients with these predictors to find the evidence and intracardiac complications of GBS IE.

**Keywords**: Echocardiography; Group B *Streptococcus*; Infective endocarditis; Septicemia; Valvular heart disease

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*Streptococcus agalactiae* or Group B *Streptococcus* (GBS), classified by the Lancefield classification[1], is a pathogen that commonly causes septicemia in pregnant women or neonates[2]. However, recent data showed that invasive GBS infections were found in a considerable proportion or about 2/3 non-pregnant adult patients[3]. The most common infection sites are skin/soft tissue infections and bacteremia without a primary focus[2].

Infective endocarditis (IE) is infection of the heart's endocardium[4], in which *Staphylococcus aureus* is one of the common pathogens. According to the recommendation of the 2015 European Society of Cardiology (ESC) Guideline for the management of IE, routine echocardiographic screening should be considered in all patients with *Staphylococcus aureus* septicemia to find evidence of IE[5]. This recommendation is based on a report that *Staphylococcus* IE is found in 22% of all *Staphylococcus* bacteremia patients, and in those who have IE, it carries a worse prognosis[6].

GBS IE is found to have high mortality and severe

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cardiac valve destruction, same as *Staphylococcus* IE[7]. On the contrary, the prevalence of GBS IE appears to be lower, at 2% to 9%[8-11]. Therefore, there is no recommendation on routine echocardiography for GBS septicemia. However, the literature review found that the studies were conducted in the late 1990s to early 2000s, except for the study by Phoompoung et al, which was published in 2021[11]. Moreover, echocardiographic data are scant.

The present study aimed to find the prevalence of GBS IE in patients with GBS septicemia and assessed the echocardiographic features, predictors, and outcomes. The present study would be helpful for developing a recommendation for echocardiography for the diagnosis of IE.

## Material and Methods

### Study design and patient collection

Patients admitted to the Department of Medicine, Siriraj Hospital, Bangkok, Thailand, between January 1, 2005 and December 31, 2019, due to GBS septicemia were enrolled in the study.

The inclusion criteria were all patients older than 18 years old with one or more samples of hemoculture positive for GBS. Patients with definite infection sites other than IE were also included in the study, as GBS IE could occur in cases with previous evidence of multi-site infection. GBS IE was diagnosed by at least one sample of hemoculture being positive for GBS within 48 hours after admission plus echocardiographic evidence of endocarditis. IE included both "definite IE", as defined by two major or one major plus three minor criteria, and "possible IE", as defined by one major and one minor criteria, according to modified Duke criteria. The decision to perform transthoracic (TTE) and transesophageal echocardiography (TEE) was up to the primary physician. Echocardiography was done with an IE33 or EPIQ CVx (Phillips, The Netherlands). The exclusion criteria were pregnant women and patients with inadequate interpretable data in their medical records.

The present research was approved by the Ethical Committee for Human Research, Faculty of Medicine, Mahidol University, the IRB number was Si 403/2021.

### Data collection

Patients were searched using the ICD-10 code A401, which is sepsis due to GBS. Two hundred seven patients with GBS septicemia were included in the present study. The patients' electronic chart records, echocardiograms, and reports were reviewed. Primary bacteremia was referred to as positive GBS in hemoculture without definite site of infection. Death was referred to as in-hospital mortality, and valvular surgery was referred to as valvular surgery due to IE, whether in-hospital or elective surgery.

The primary outcome measure here was the prevalence of GBS IE in the GBS septicemic patients. The secondary outcomes were the echocardiographic features, predictors, and outcomes such as in-hospital death and a composite of in-hospital death and valvular surgery, of GBS IE.

### Statistical analysis

All the analyses were performed using IBM SPSS Statistics for Macintosh, version 26 (IBM Corp., Armonk, NY, USA). The normally distributed continuous variables were described by the mean ± standard deviation (SD). The non-normally distributed continuous variables were reported as the median with interquartile range (IQR). The student's t-test was used to compare normally distributed data, and the Mann-Whitney U test was used for non-normally distributed data. The categorical variables were presented as the number of cases and percentage. The chi-square or Fisher's exact test was used to determine whether a difference existed between groups. A p-value of lower than 0.05 was considered as showing statistical significance. Factors that had statistical significance were further analyzed by multivariate analysis using multiple logistic regression analysis and backward stepwise method, to determine the predictors of GBS IE in GBS septicemia. Data were expressed as the odds ratio (OR) and 95% confidence interval (CI).

## Results

Two hundred seven patients were included in the present study. The prevalence of GBS IE was 22 out of the 207 patients (10.6%, 95% CI 6.8 to 15.6). Table 1 shows the baseline characteristics, clinical presentation, and clinical infectious syndrome of the patients.

The authors performed univariate analysis of the statistically significant factors, and the variables that reached the $p<0.10$ were included in the multivariate analyses. There were three factors, namely age (adjusted OR 0.95, 95% CI 0.91 to 0.99; $p=0.012$), new murmur (adjusted OR 91.62, 95% CI 20.12 to 417.16; $p<0.001$), and stroke/systemic embolism (SE) (adjusted OR 17.94, 95% CI 1.79 to 179.49; $p=0.014$) that had an independent predictive value for GBS IE in the GBS septicemic patients, as shown in Table 2.

There was no significant difference regarding death between the IE and the non-IE group at 9.1%

**Table 1.** Baseline characteristics, presenting symptoms, and clinical infectious syndrome

| | All (n=207) | No IE (n=185) | IE (n=22) | p-value |
|---|---|---|---|---|
| Age (years); mean±SD | 62.1±17.1 | 63.0±17.1 | 54.2±14.5 | 0.022 |
| Sex: male; n (%) | 101 (48.8) | 93 (50.3) | 8 (36.4) | 0.217 |
| Height (cm); mean±SD | 159.5±9.3 | 159.3±9.6 | 160.3±7.8 | 0.644 |
| Weight (kg); mean±SD | 60.2±13.4 | 59.9±12.5 | 62.0±17.9 | 0.512 |
| Body surface area ($m^2$); mean±SD | 1.6±0.2 | 1.6±0.2 | 1.6±0.2 | 0.675 |
| Diabetes mellitus; n (%) | 60 (29.0) | 56 (30.3) | 4 (18.2) | 0.237 |
| Hypertension; n (%) | 96 (46.4) | 93 (50.3) | 3 (13.6) | 0.001 |
| End stage renal disease; n (%) | 12 (5.8) | 12 (6.5) | 0 (0.0) | 0.371 |
| Coronary arterial disease; n (%) | 19 (9.2) | 17 (9.2) | 2 (9.1) | 1.000 |
| Chronic obstructive pulmonary disease; n (%) | 7 (3.4) | 7 (3.8) | 0 (0.0) | 1.000 |
| Cancer; n (%) | 11 (5.3) | 10 (5.4) | 1 (4.5) | 1.000 |
| Rheumatic heart disease; n (%) | 1 (0.5) | 0 (0.0) | 1(4.5) | 0.106 |
| Cirrhosis; n (%) | 16 (7.7) | 16 (8.6) | 0 (0.0) | 0.228 |
| Immunosuppressive drugs; n (%) | 11 (5.3) | 11 (5.9) | 0 (0.0) | 0.611 |
| Valvular heart disease; n (%) | 8 (3.9) | 7 (3.8) | 1 (4.5) | 0.600 |
| History of valve replacement; n (%) | 10 (4.8) | 9 (4.9) | 1 (4.5) | 1.000 |
| Intravenous drug use; n (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) | N/A |
| Previous IE; n (%) | 1 (0.5) | 1 (0.5) | 0 (0.0) | 1.000 |
| Presence of CIED; n (%) | 4 (1.9) | 4 (2.2) | 0 (0.0) | 1.000 |
| Old stroke; n (%) | 18 (8.7) | 17 (9.2) | 1 (4.5) | 0.700 |
| Presenting symptoms; n (%) | | | | |
| Fever | 187 (90.3) | 165 (89.2) | 22 (100) | 0.139 |
| Dyspnea | 25 (12.1) | 19 (10.3) | 6 (27.3) | 0.033 |
| New murmur | 32 (15.5) | 13 (7.0) | 19 (86.4) | <0.001 |
| Vascular phenomenon | 2 (1.0) | 0 (0.0) | 2 (9.1) | 0.011 |
| Immunologic phenomenon | 2 (1.0) | 1 (0.5) | 1 (4.5) | 0.202 |
| Heart failure | 14 (6.8) | 9 (4.9) | 5 (22.7) | 0.009 |
| Septic shock | 36 (17.4) | 32 (17.3) | 4 (18.2) | 1.000 |
| Stroke/SE | 10 (4.8) | 4 (2.2) | 6 (27.3) | <0.001 |
| Confusion | 35 (16.9) | 35 (18.9) | 0 (0.0) | 0.030 |
| Eye pain | 4 (1.9) | 4 (2.2) | 0 (0.0) | 1.000 |
| Clinical infectious syndrome; n (%) | | | | |
| Skin/soft tissue infection | 44 (21.3) | 43 (23.2) | 1 (4.5) | 0.052 |
| Pneumonia | 8 (3.9) | 8 (4.3) | 0 (0.0) | 1.000 |
| Osteomyelitis | 4 (1.9) | 4 (2.2) | 0 (0.0) | 1.000 |
| Arthritis | 53 (25.6) | 44 (23.8) | 9 (40.9) | 0.082 |
| Urosepsis | 4 (1.9) | 4 (2.2) | 0 (0.0) | 1.000 |
| Peritonitis | 2 (1.0) | 2 (1.1) | 0 (0.0) | 1.000 |
| Meningitis | 35 (16.9) | 31 (16.8) | 4 (18.2) | 0.771 |
| Catheter related | 1 (0.5) | 1 (0.5) | 0 (0.0) | 1.000 |
| Endophthalmitis | 7 (3.4) | 6 (3.2) | 1 (4.5) | 0.534 |
| Primary bacteremia | 60 (29.0) | 60 (32.4) | 0 (0.0) | 0.002 |

CIED=cardiovascular implantable electronic device; IE=infective endocarditis; N/A=not applicable; SD=standard deviation; SE=systemic embolism

versus 14.1% (p=0.745). However, if valve surgery was included in the composite outcome, the IE group had significantly worse outcomes than the non-IE group at 63.6% versus 14.1% (p <0.001), as shown in Figure 1.

TTE and TEE were done in 82 (39.6%) and 19 (9.2%) out of the 207 patients, respectively. TTE was done in 20 out of the 22 patients (90.9%) in the IE group when compared with 62 out of the 185 patients (33.5%) in the non-IE group, p<0.001. TEE

**Table 2.** Univariate and multivariate analysis of the predictors for GBS IE in the GBS septicemic patients

| Variable | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | Crude OR | 95% CI | p-value | Adjusted OR | 95% CI | p-value |
| Age | 0.97 | 0.95 to 1.00 | 0.025 | 0.95 | 0.91 to 0.99 | 0.012 |
| Dyspnea | 3.28 | 1.15 to 9.38 | 0.027 | | | |
| Murmur | 83.76 | 21.90 to 320.60 | <0.001 | 91.62 | 20.12 to 417.16 | <0.001 |
| HF | 5.75 | 1.73 to 19.12 | 0.004 | | | |
| Stroke/SE | 16.97 | 4.34 to 66.41 | <0.001 | 17.94 | 1.79 to 179.49 | 0.014 |
| Arthritis | 2.22 | 0.89 to 5.54 | 0.088 | | | |

CI=confidence interval; HF=heart failure; OR=odds ratio; SE=systemic embolism

**Table 3.** Echocardiographic parameters according to the absence or presence of IE

| | All (n=82); mean±SD | No IE (n=62); mean±SD | IE (n=20); mean±SD | p-value |
|---|---|---|---|---|
| LVEDV (mL) | 73.6±30.0 | 71.7±30.3 | 79.4±29.2 | 0.350 |
| LVESV (mL) | 26.8±17.4 | 26.7±18.9 | 27.2±12.1 | 0.924 |
| LVEF (%) | 65.2±9.0 | 65.1±9.6 | 65.8±6.7 | 0.761 |
| LVDd (mm) | 42.1±8.9 | 42.0±7.7 | 42.3±11.9 | 0.932 |
| LVDs (mm) | 27.4±6.7 | 27.4±6.5 | 27.5±7.5 | 0.954 |
| LV mass index (g/m$^2$) | 95.8±27.1 | 94.5±23.3 | 99.4±36.5 | 0.660 |
| RWT | 0.6±0.2 | 0.6±0.2 | 0.6±0.3 | 0.738 |
| LA volume index (mL/m$^2$) | 41.5±18.9 | 42.1±18.6 | 40.0±20.3 | 0.692 |
| TAPSE (mm) | 21.8±4.7 | 21.3±4.5 | 23.3±5.2 | 0.221 |
| Peak lateral TV annulus velocity (cm/s) | 12.2±2.4 | 11.8±2.3 | 13.1±2.7 | 0.176 |
| RAP (mmHg) | 8.3±3.1 | 8.2±3.1 | 8.6±3.0 | 0.663 |
| RVSP (mmHg) | 40.0±14.1 | 40.0±14.3 | 39.9±14.4 | 0.992 |
| Mean PAP (mmHg) | 28.0±7.9 | 26.9±7.3 | 32.1±9.3 | 0.152 |

LA=left atrium; LV=left ventricle; LVDd=left ventricular diastolic dimension; LVDs=left ventricular systolic dimension; LVEDV=left ventricular end diastolic volume; LVEF=left ventricular ejection fraction; LVESV=left ventricular end systolic volume; PAP=pulmonary artery pressure; RAP=right atrial pressure; RVSP=right ventricular systolic pressure; RWT=relative wall thickness; SD=standard deviation; TAPSE=tricuspid annular plane systolic excursion; TV=tricuspid valve

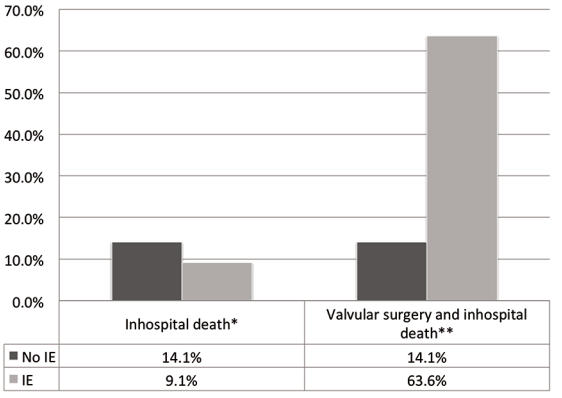


**Figure 1.** Outcomes according to the absence or presence of IE.

* p=0.745, ** p<0.001, IE=infective endocarditis

was done in 15 out of the 22 patients (68.2%) in the IE group when compared with four out of the 185 patients (2.2%) in the non-IE group, p<0.001. Overall, TTE and TEE were done more frequently in the IE group than in the non-IE group. However, there was no significant difference in the echocardiographic parameters between the IE and non-IE group, as shown in Table 3.

The features of vegetation and intracardiac complications in the IE group are presented in Table 4. In addition, 13 patients underwent both TTE and TEE, among whom, three patients (23.1%) had echocardiographic signs of IE that were only seen on TEE but not on TTE.

The most common valve that was affected by the infecting organism was the mitral valve, followed by the aortic valve. Three patients had double-valve involvement and included two patients that had aortic valve and mitral valve involvement and one patient that had aortic valve and tricuspid valve involvement. Vegetation was detected in 18 out of 22 patients (81.8%). GBS IE caused significant at the moderate

**Table 4.** The features of vegetation and intracardiac complications in the IE group

| Echocardiographic features | n=22 |
|---|---|
| Site of valve involvement (25 lesions); n (%) | |
| Mitral valve | 15 (60.0) |
| Aortic valve | 9 (36.0) |
| Tricuspid valve | 1 (4.0) |
| Vegetation; n (%) | 18/22 (81.8) |
| Size of intracardiac mass (cm); median (IQR) | 1.1 (0.6, 1.9) |
| Regurgitation degree; n (%) | |
| No | 1 (4.5) |
| Mild | 6 (27.3) |
| Moderate | 2 (9.1) |
| Severe | 13 (59.1) |
| Intracardiac complications (10 lesions); n (%) | 8/22 (36.4) |
| Abscess | 1/10 (10.0) |
| Pseudoaneurysm | 2/10 (20.0) |
| Fistula | 1/10 (10.0) |
| Perforation | 6/10 (60.0) |

IQR=interquartile range

or higher level, valvular regurgitation and intracardiac IE complications in 2/3 and 1/3 patients, respectively. Two patients had two complications, which were pseudoaneurysm with fistula and pseudoaneurysm with valve perforation. There were two in-hospital deaths (9.1%) and 12 patients (54.5%) underwent valve surgery, with the median day of valve surgery being 62.5 days after IE was diagnosed.

## Discussion

The authors present the results of 207 patients admitted to Siriraj Hospital due to GBS septicemia. The overall prevalence of GBS IE was 22 out of the 207 patients (10.6%). The prevalence of IE in the present study was higher than in the previous reports by Farley et al at 2%[8], Skoff et al at 3%[9], Schwartz et al at 9%[10], and Phoompoung et al at 5.3%[11]. However, these studies had the proportion of patients with GBS septicemia at 71% to 94%, unlike in the present study report, which included only those patients with GBS septicemia. Moreover, these studies did not comment on the echocardiographic features and the frequency of the patients that had echocardiography done. In the present study, only 82 out of the 207 patients (39.6%) had TTE and even less had TEE done at 19 out of the 207 patients (9.2%). The authors believe that this prevalence may be underestimated due to echocardiography, which was the primary investigation for IE diagnosis, being done infrequently. However, when compared to the present study results, the prevalence of GBS IE in GBS septicemia was at least about a half of *Staphylococcus aureus* IE in *Staphylococcus aureus* septicemia[6]. Regarding the clinical presentation, there were significantly more incidences of new murmur, dyspnea, heart failure, vascular phenomenon, and stroke in the GBS IE group compared with the non-IE group. On the contrary, the GBS IE group was on the average younger than the non-IE group. The authors performed multivariate analysis and demonstrated that age, new murmur, and stroke/SE were predictors of GBS IE in the GBS septicemic patients, with ORs of 0.95, 91.62, and 17.94, respectively. These findings may have a clinical value to identify high-risk patients needed to be intensely investigated.

Regarding the secondary outcome, two patients died (9.1%), and 12 patients (54.5%) underwent valve surgery. Compared with the previous report by Sambola et al. and their review of 30 cases and the literature between 1962 to 1998[7], the present study has a lower mortality rate at 9.1% versus 47%. The authors believe that this may be due to the improvement in medical treatment and the higher rate of valvular surgery in the present study at 54.5% versus 40%. In addition, the higher population of patients with a prosthetic valve IE (16.7%) in the Sambola et al report, compared to only one prosthetic valve IE (4.5%) in the present study, may be the other cause of the higher mortality rate than in the present study. Even though the present research could not demonstrate a difference in mortality rate between the IE and non-IE groups, the composite of in-hospital death and valve surgery was significantly higher in the IE group than in the non-IE group at 63.6% versus 14.1%. This evidence indicated that GBS IE carries a bad prognosis for significant valvular destruction that needs to be corrected by surgery.

According to the echocardiographic parameters, there was no significant difference between the IE and non-IE groups. Concerning the echocardiographic features of IE in the 22 patients in the GBS IE group, the most common valve involvement was the mitral valve at 60%, followed by the aortic valve at 36%. These findings were consistent with the previous reports[7]. The uniqueness of the present study was that the authors could identify a sizable proportion of IE patients with intracardiac complications at 36.4%, combined with a high rate of significant valvular regurgitation at 68.2%. This evidence highlights the virulence of this organism. TEE should

be considered as a further investigation in highly suspicious patients with a negative TTE due to the lower sensitivity of TTE, as shown in the present study results in which three out of 13 patients (23.1%) had echocardiographic signs of IE that could only be seen on TEE but not on TTE.

The authors expected that the present study data might prompt further hypothesis-generating study in upcoming research in this specific condition, which may affect the future guideline's recommendation for echocardiography in GBS septicemic patients or even the definition of the typical organism required for the IE diagnosis.

## Limitation

There were limitations in the present study to note. First, the study design was a retrospective descriptive study. This may have led to confounding factors that could not be recognized or missed and somehow may have affected the prevalence and outcomes. In addition, physical signs, such as skin signs, vascular phenomenon, and immunologic phenomenon, were prone to be overlooked according to the current study design. Second, as previously mentioned, the present study patients had TTE done in only one-third of all cases and TEE done in only one-tenth. This is in contrast with the study of *Staphylococcus aureus* septicemia by Rasmussen et al[6], where all the patients had either TTE or TEE. This may have led to underestimating the prevalence in the present study. Third, the sample size was too small. While there was a trend that clinical arthritis syndrome may be associated with increased IE prevalence, the authors could not demonstrate statistical significance. Furthermore, the low IE event rate could have caused uncertainty in the estimates of the association in the multivariate analysis.

## Conclusion

The present study demonstrated that the prevalence of GBS IE in GBS septicemia was 10.6%. Age, new murmur, and stroke/SE were independent predictors of GBS IE in GBS septicemic patients. GBS IE was found to be a severe condition that caused a sizable proportion of intracardiac complications and valvular regurgitation. GBS IE was also associated with a significantly higher rate of composite events of in-hospital mortality and valve surgery.

## What is already known on this topic?

The prevalence of GBS IE in invasive GBS infection was 2% to 9%.

## What this study adds?

The present study demonstrated the prevalence of GBS IE in GBS septicemia in the recent era. The study included the outcome, predictors, and echocardiographic features of GBS IE that have been scantly described in the previous reports.

## Conflicts of interest

The authors declare they have no conflicts of interest.

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