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# Clinical and microbiological characteristics of recurrent group B streptococcal infection among non-pregnant adults

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SUMMARY

*Objective:* This study aimed to investigate the clinical and microbiological features of recurrent group B streptococcal (GBS) diseases among non-pregnant adults.
*Methods:* All hospitalized non-pregnant adults who had culture-proven GBS infections between January 2008 and December 2010 were enrolled in this retrospective study. Bacterial isolates were examined for their serotypes, genotypes, and antimicrobial resistance.
*Results:* The recurrence rate of GBS infection in Taiwan was found to be 9.3%. Of the 70 recurrent episodes in 32 patients, infections of the urinary tract (U) were diagnosed clinically in 55.7%, infections of the soft tissue (S) in 31.4%, and infections of the bloodstream (B) in 12.9%. The initial/recurrent episodes in 25 patients were mainly U/U (40.6%), followed by S/S (18.8%) and B/B (6.2%). The serotypes/serogroups identified were serotypes V (34.3%), Ib (22.9%), VI (17.1%), III (12.9%), IV (7.1%), and Ia (5.7%). Recurrent strains showed less resistance to erythromycin or clindamycin than non-recurrent strains. Six distinct genotypes were identified in 12 serotype VI isolates derived from seven patients; five of these isolate pairs had identical genotypes.
*Conclusions:* Recurrent GBS diseases were found to occur considerably more often than previously thought, mainly in adults with a high comorbid index. Relapse, not new acquisition, was found to be more common.


## 1. Introduction

Invasive group B streptococcal (GBS) diseases in non-pregnant adults represent a substantial and increasing health burden worldwide, particularly in the elderly and those with comorbidities.[1–4] Diabetes mellitus, cirrhosis, renal failure, cancer, and decubitus ulcers are independent risk factors for invasive GBS diseases in non-pregnant adults.[4,5] Common clinical presentations in these patients include skin and soft tissue infections, bacteremia, pneumonia, and urinary tract infections.[6] The worldwide development of antimicrobial resistance to macrolides, lincosamides, and fluoroquinolones and the emergence of penicillin resistance in GBS has limited the use of these antibiotics to treat certain infections.[7–9]

The recurrence of GBS infections, first reported in the mid to late 1970s, remains a rare manifestation of pediatric and adult GBS infections.[10,11] Although little is known about this phenomenon, two population-based surveillance studies in Denmark and North America demonstrated the recurrence rate to be 1.3% for children and 4.3% for adults.[11,12] Predicting which patients among those

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with an initial GBS infection will develop disease recurrence is challenging. In fact, patients with recurrent GBS infections clinically resemble patients with their first GBS infection. Data describing the clinical and microbiological features of recurrent GBS infection in adults, including risk factors to predict recurrence, are lacking. Whether a tendency exists in strain-specific characteristics that contribute markedly to recurrence also remains unknown.

This study investigated the clinical characteristics of recurrent GBS infections, specifically with respect to grading systems that accurately predict recurrence. This study also identified the capsular serotypes, resistance phenotypes, and pulsed-field gel electrophoresis (PFGE) genotypes of the clinical isolates causing recurrent infections.

## 2. Materials and methods

### 2.1. Patients and isolates

All hospitalized non-pregnant adults who had culture-proven GBS infections between January 2008 and December 2010 were enrolled in this retrospective study. A recurrent GBS infection was defined as a new culture-proven GBS infection that occurred more than 1 month after completion of antimicrobial therapy for the initial infection in the same individual.[13] Patients with nosocomial infections were ineligible when they had hospital-acquired GBS infections. Clinical isolates of GBS were identified by standard laboratory techniques, in accordance with the guidelines of the US Centers for Disease Control and Prevention (CDC; 2010),[14] at the Department of Laboratory Medicine, Chang Gung Memorial Hospital (CGMH), Chiayi, which is a 1300-bed tertiary care teaching hospital located in southern Taiwan. All clinical isolates of GBS were selected using Todd–Hewitt broth (Oxoid, UK) supplemented with colistin (10 μg/ml) and nalidixic acid (15 μg/ml) (bioMérieux, France) in order to prevent growth of contaminants. All suspected GBS colonies (pin point, with narrow beta-hemolysis) were sub-cultured on blood agar and subjected to Gram staining and catalase tests. All Gram-positive and catalase-negative cocci isolates were confirmed using the Christie, Atkins, Munch-Peterson (CAMP) test and latex agglutination assay.[15] This study was approved by the research ethics committee of CGMH. The serotype and serogroup (ST/SG) of each isolate were determined using a multiplex PCR assay, as described previously.[16]

### 2.2. Clinical information

The medical charts of each patient were reviewed and the following data collected: demographics, comorbid conditions, hospitalization history, definitive antibiotic regimens, duration of antibiotic treatment, final diagnosis, and outcome. The Charlson comorbidity index (CCI) is a weighted-score scale based on the relative risk of 19 conditions that significantly influence outcome.[17] Patients were considered to have a comorbid condition when they had a listed disorder in their records or were treated for the disorder. The CCI scores were calculated by weighting each comorbid disease independently.

### 2.3. Antimicrobial susceptibility

All isolates were screened for susceptibility to erythromycin and clindamycin using double disk diffusion tests. Macrolide–lincosamide–streptogramin B ($MLS_B$) phenotypes were characterized as described previously.[18] Macrolide phenotypes (M) were categorized by susceptibility to clindamycin without blunting inhibition zones around the clindamycin disk. The minimum inhibitory concentration (MIC) of dalfopristin was applied to identify the lincosamide–streptogramin A (LSA) phenotypes in isolates with erythromycin susceptibility and clindamycin resistance. Resistance to erythromycin, clindamycin, and dalfopristin was identified using the agar dilution method with the breakpoints of the Clinical and Laboratory Standards Institute.[19]

### 2.4. DNA preparation and PFGE

Macrofragments of genomic DNA from serotype VI isolates, digested with *Sma*I (New England BioLabs, Frankfurt, Germany), were analyzed by pulsed-field gel electrophoresis (PFGE), as described previously.[20] The total number of visible bands was counted for each isolate, and patterns were compared visually. Genotypes and subtypes were verified using the criteria of Tenover et al.[21]

### 2.5. Statistical analysis

Categorical data were analyzed using the Chi-square test or Fisher's exact test. Continuous variables were analyzed using the Student's *t*-test. Univariate and multivariate logistic regression analysis was used to discriminate independent risk factors of comorbid conditions. All data were analyzed using IBM–SPSS v. 20.0 software (IBM Corp., Armonk, NY, USA). Two-sided *p*-values $<0.05$ were considered to be statistically significant.

## 3. Results

### 3.1. Demographics

In total, 345 individuals had 383 episodes of GBS infection, and recurrent infections were detected in 32 patients (70 episodes); thus, the recurrence rate was 9.3% (32/345). The mean age of the 345 patients was 57.7 years (range 18–92 years) when they had their first GBS infection (Table 1). No difference in gender distribution was found between the two groups of patients.

### 3.2. Comorbid conditions

In total, 165 (47.8%) of the 345 patients had a CCI score $\geq 1$. The most common comorbid condition encountered in recurrence was diabetes (31.2%), followed by diabetes with end-organ damage (18.8%), peptic ulcer disease (15.6%), any prior tumor (9.4%), and moderate to severe renal disease (9.4%) (Table 1). Although diabetes with end-organ damage was a risk factor for recurrence ($p = 0.012$), multivariate analysis showed that diabetic patients with and without end-organ damage had a higher risk for recurrent infections than non-diabetic patients (16.7% (16/96) vs. 6.4% (16/249); $p = 0.003$) (odds ratio 2.913, 95% confidence interval 1.392–6.092; $p = 0.005$) (data not shown).

The weighted scores of all comorbid conditions were summed and then scaled to the CCI. The mean CCI of recurrence patients was significantly higher than that of non-recurrence patients ($1.88 \pm 1.91$ vs. $1.11 \pm 1.58$; $p = 0.011$).

### 3.3. Clinical diagnosis and time intervals

The clinical diagnosis of the 70 recurrent infections was 39 urinary tract infections (55.7%) (U), 22 soft tissue infections (31.4%) (S), and nine bloodstream infections (12.9%) (B) (Table 2). Twenty-five (78.1%) of the 32 patients had similar clinical presentations for consecutive episodes of GBS infection, mainly U/U (40.6%), followed by S/S (18.8%), B/B (6.2%), S/B (6.2%), U/U/U (6.2%), and S/S/S (6.2%). Primary bacteremia was found in patients in the B/B, U/B, and U/U/B groups. Soft tissue infection with bacteremia was categorized into the bloodstream infection (B)