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The clinical and molecular characteristics of invasive *Streptococcus agalactiae* diseases in nonpregnant adults in Taiwan

Jen-Fu Hsu [b,d], Wei-Ju Lee [b,d], Shih-Ming Chu [b,d], Yao-Sheng Wang [b,d], Hsuan-Rong Huang [b,d], Peng-Hong Yang [b,d], Jang-Jih Lu [c,**], Ming-Horng Tsai [a,d,*]

[a] *Division of Neonatology and Pediatric Hematology/Oncology, Department of Pediatrics, Chang Gung Memorial Hospital, Yunlin, Taiwan*
[b] *Division of Pediatric Neonatology, Department of Pediatrics, Chang Gung Memorial Hospital, Taoyuan, Taiwan*
[c] *Division of Clinical Pathology, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, New Taipei City, 23142, Taiwan*
[d] *School of Medicine, College of Medicine, Chang Gung University, Taoyuan, Taiwan*

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ABSTRACT

Background: *Streptococcus agalactiae* (Group B *Streptococcus*, GBS) is a growing threat to nonpregnant adults. We aimed to describe the clinical and molecular characteristics of invasive GBS infections in adults.
Methods: All adults with invasive GBS infections at a tertiary-level medical center in Taiwan between 2014 and 2020 were analyzed. Capsule serotyping, multilocus sequence typing and antibiotic susceptibility testing were performed.
Results: A total of 666 adults with GBS infections were analyzed. The median age at onset was 65 years (range 19–102). The most common manifestation was bacteremia without focus (80.4 %). The younger patients (19–39 years old) had a significantly higher rate of non-bloodstream infections (24.6 %, $P < 0.001$) and were overweight in most cases (77.2 %). Most patients had underlying chronic comorbidities (82.3 %). Capsular types VI (33.0 %), Ia (19.4 %), III (15.0 %), and V (10.2 %) were predominant. Clonal complexes (CCs) 1, 12, 17, 19, 23 and 452 accounted for 96.3 % (464/482) of the cases. All GBS isolates were susceptible to β-lactam antibiotics. The rates of resistance to erythromycin and clindamycin were 42.6 % and 39.2 %, respectively, but were especially high in type III, Ib and V GBS isolates. The mortality rates at one month and one year were 5.0 % and 12.3 %, respectively, but were significantly higher in elderly patients.
Conclusion: The clinical manifestations of invasive GBS infections in adults are diverse. Elderly patients are susceptible to invasive GBS infections and have a relatively high mortality rate. Continuous surveillance of GBS epidemiology should be enforced given the increasing growing importance of antibiotic-resistant GBS isolates.

1. Introduction

The opportunistic pathogen *Streptococcus agalactiae* (Group B *Streptococcus*, GBS) is a commensal bacterium that colonizes the genitourinary and digestive tracts in 20–30 % of healthy adult humans.[1,2] GBS is an important pathogen that causes neonatal sepsis and meningitis,[3] and invasive GBS infections are now increasingly common in elderly individuals.[4] The incidence of invasive GBS infections in adults has increased in several European countries, the United States of America and Southeast Asia.[3–5] Risk factors for invasive GBS infections in adults include immunocompromised status, malignancy, diabetes, obesity, and multiple chronic comorbidities.[4–6] The majority of elderly patients with invasive GBS infections require hospitalization, and a significant proportion of them are treated in intensive care units (ICUs).[7,8] In contrast to the extensive characterization of invasive GBS infections in neonates, relatively few data on adult GBS infections are available in the literature.

Common clinical manifestations of adult GBS infections include bacteremia without focus, soft tissue infections, osteomyelitis and urinary tract infection.[6,9,10] Some elderly patients who present with septic shock, meningitis, pneumonia and endocarditis often have multiple chronic comorbidities and are at high risk for final mortality.[11,12] The molecular epidemiology of invasive GBS infections in adults varies greatly among different geographic areas and is often quite different from that of invasive infections in neonates.[12–15] GBS serotypes Ia, Ib, II,

* Corresponding author. Division of Neonatology and Pediatric Hematology/Oncology, Department of Pediatrics, Chang Gung Memorial Hospital, Yunlin, Taiwan.
** Corresponding author. Division of Clinical Pathology, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, New Taipei City, 23142, Taiwan.
E-mail addresses: janglu45@gmail.com (J.-J. Lu), mingmin.tw@yahoo.com.tw (M.-H. Tsai).

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and V are commonly reported in most countries, and the serotype IV GBS strain has been reported emergently in some studies.[16,17] We aimed to investigate the clinical and microbiological features and outcomes of invasive GBS infections in nonpregnant adults at a tertiary medical center in Taiwan. Additionally, concurrent conditions, chronic comorbidities, prior medical history and prior surgery within three months before diagnosis, and outcomes (including all-cause mortality within one month and one year after invasive GBS infections) were characterized in the cohort.

2. Methods

2.1. GBS isolates, data collection and definition

A cohort study involving all adults with invasive GBS infections who were hospitalized at Linkou Chang Gung Memorial Hospital (CGMH) between 2014 and 2020 was conducted by our research team. Invasive GBS infections were defined when positive GBS cultures were isolated from normally sterile sites, including blood; cerebrospinal fluid; pleural, peritoneal, and synovial fluids; ascites; and deep tissue. Only patients ≥18 years of age were enrolled, and pregnant women who delivered within 30 days of the bacterial isolate sample were also excluded. All GBS isolates were retrieved from Linkou CGMH's central laboratory and bacterial library. All the GBS isolates were identified to be catalase-negative gram-positive cocci and had a narrow zone of β-hemolytic colonies on a sheep blood agar plate, a positive reaction on the Christie/Atkins/Munch–Peterson test, and Lancefield Group B antigen in the cell wall. The clinical information of all the patients, including patient demographics, underlying chronic comorbidities, clinical features, hospital courses, treatments and outcomes, was retrospectively reviewed and recorded by our research teams. This study was approved by the Institutional Review Board of CGMH (IRB No. 202101785B1), and a waiver for informed consent for anonymous data collection was approved.

We defined severe sepsis, septic shock and uncomplicated bacteremia on the basis of the Third International Consensus Definitions for Sepsis and Septic Shock.[18,19] Specimens from the skin surface, artificial devices and some nonsterile sites were not included in the analyses. All duplicate GBS isolates from the same patient during the same infection episode, whether from the same or different sources, were excluded from the analyses. Polymicrobial infection was considered to be present when only one of multiple bacterial isolates from sterile sites was GBS. For patients with more than two episodes of invasive GBS infections, only the first episode was included in the analyses. Obesity was defined on the basis of body mass index (BMI), with a BMI ≥27 being considered obese. Because most patients had underlying chronic comorbidities, the final outcomes were all-cause mortality within one month and one year after the onset of invasive GBS disease.

2.2. Capsular serotyping and MLST

The capsular serotypes of all GBS isolates were analyzed using the multiplex PCR to identify GBS isolates of types Ia to IX.[20,21] The capsule gene typing method was based on the standard protocols described in previous publications.[20–23] A multiplex PCR assay for the identification of serotypes Ia to IX of GBS isolates was developed on the basis of the method described by Imperi et al.[21] Briefly, a single PCR mixture containing 19 primers was used in the multiplex PCR assay. Therefore, an analysis of the unique two- or three-band pattern on a 1 % agarose gel (SeaKem ME agarose; Lonza) could be used to identify each serotype. Agarose gel electrophoresis was used to analyze the amplicons, and the presence of DNA fragments of the same size as in one of the strains with known serotypes was used to establish the capsular gene type. A representative sample of GBS Isolates (representing approximately 70–75 % of the cases) was randomly selected for multilocus sequence typing (MLST) analyses. The DNA isolation method and PCR were used to amplify and sequence seven housekeeping genes (*adhP*, *atr*, *glcK*, *glnA*, *pheS*, *sdhA*, and *tkt*), after which MLST was performed.[22] After PCR, the sequence type (ST) was assigned on the basis of the allelic profile of each fragment and determined via the *Streptococcus agalactiae* MLST database (http://pubmist.org/sagalactiae). All GBS isolates can be clustered into several major CCs on the basis of the goeBURST program.[24]

2.3. Antimicrobial susceptibility testing

The disk diffusion method was used to test the antimicrobial susceptibility of all the GBS isolates, as described in previous studies.[25] We used the double-disk diffusion test to identify inducible clindamycin resistance. The double-disk diffusion test (D test) was applied to identify inducible clindamycin resistance. An erythromycin disc was placed 15 mm–26 mm (edge to edge) from a clindamycin disc in a standard disk diffusion test. After incubation, a flattening of the zone in the area near the clindamycin disc indicates that the GBS isolate has inducible clindamycin resistance and tests positive on the D test. All GBS isolates were tested for susceptibility to seven antibiotics, including erythromycin, penicillin, clindamycin, vancomycin, ampicillin, cefotaxime and teicoplanin, according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI) for the disc diffusion method.[26]

2.4. Statistical analysis

The clinical and genetic characteristics of different serotypes of GBS isolates that caused invasive infections in adults during the study period were compared. Categorical and continuous variables are expressed as proportions and medians (interquartile ranges, IQRs), respectively. Categorical variables were compared using the χ^2 test or Fisher's exact test; odds ratios (ORs) and 95 % confidence intervals (CIs) were calculated. The chi-square test or Fisher's exact test was used to investigate the associations between capsular typing and MLST in all GBS isolates. Continuous variables were compared using the Mann−Whitney *U* test and the *t*-test, depending on their distributions. The trend of the proportions of the categorical variables among the subgroups was analyzed with the Cochran−Armitage trend test. The results with P values of <0.05 were considered statistically significant. All the statistical analyses were performed using SPSS version 23 (IBM SPSS Statistics).

3. Results

3.1. Patient characteristics and clinical manifestations

During the study period, a total of 666 adult patients with invasive GBS infections were identified, and all GBS isolates were extracted from the central laboratory of Linkou CGMH for analysis. A total of 15.0 % (n = 100) of these patients were from the intensive care unit. The GBS isolates were mainly from blood cultures (535 of 666, 80.3 %), followed by deep tissue abscesses (n = 63, 9.5 %), synovial fluid from joint or bone biopsies (n = 31, 4.7 %), abdominal fluid (n = 14, 2.1 %), pleural fluid (n = 10, 1.5 %), urine culture (n = 5, 0.8 %) and cerebrospinal fluid (n = 5, 0.8 %). There were two cases of endocarditis and one case of postpartum endometritis in the cohort.

The patients' demographics are summarized in Table 1. There were slightly more female patients (51.8 %) than male patients. The median age of the cohort was 65 years (IQR, 53–78 years; range, 19–102 years). Most of the patients had underlying chronic comorbidities (n = 355, 82.3 %), including hypertension (50.3 %), malignancy (42.5 %) and diabetes (40.5 %). Hypertension and hyperlipidemia were significantly more common among older patients aged ≥85 years. The percentage of obese individuals (48.8 %) in the cohort was comparable to that in the general population of Taiwanese adults. However, a very high percentage of younger patients (19–39 years old) were obese (77.2 %). Additionally, 34.5 % (n = 255) had more than one chronic comorbidity (see Table 2).

The infectious foci and clinical manifestations were comparable

Table 1
Patient demographics and clinical features of adults with group B Streptococcus (GBS) invasive diseases from Chang Gung Memorial Hospital (CGMH), 2014–2020.

	All cases (total n = 666)	18–39 years old (n = 57, 8.6 %)	40–64 years old (n = 274, 41.1 %)	65–84 years old (n = 243, 36.5 %)	≥85 years old (n = 92, 13.8 %)
Gender					
Male	321 (48.2)	26 (45.6)	142 (51.8)	107 (44.0)	46 (50.9 %)
Female	345 (51.8)	31 (54.4)	132 (48.1)	136 (56.0)	46 (50.9 %)
Hospitalization					
General wards	566 (85.0)	51 (89.5)	234 (85.4)	211 (86.8)	70 (76.1)[a]
Intensive care units	100 (15.0)	6 (10.5)	40 (14.6)	32 (13.2)	22 (23.9)[a]
Infectious focus					
Bacteremia without other focus	535 (80.3)	35 (61.4)[a]	216 (78.8)	196 (80.7)	88 (95.7)[a]
Osteoarticular infection	31 (4.7)	3 (5.3)	11 (4.0)	15 (6.2)	2 (2.2)
Skin and soft tissue infection	63 (9.5)	7 (12.3)	29 (10.6)	27 (11.1)	0 (0.0)[a]
Intra-abdominal infection	14 (2.1)	3 (5.3)	6 (2.2)	4 (1.6)	1 (1.1)
Pneumonia	10 (1.5)	2 (3.5)	7 (2.2)	0 (0.0)	1 (1.1)
Urinary tract infection	5 (0.8)	2 (3.5)	3 (1.1)	0 (0.0)	0 (0.0)
Meningitis	5 (0.8)	3 (5.3)	2 (0.7)	0 (0.0)	0 (0.0)
Endocarditis	2 (0.3)	1 (1.8)	0 (0.0)	1 (0.4)	0 (0.0)
Others[c]	1 (0.2)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Underlying chronic comorbidities					
Diabetes mellitus	270 (40.5)	9 (15.8)[a]	105 (38.3)	116 (47.7)	40 (43.5)
Obesity	325 (48.8)	44 (77.2)[a]	141 (51.5)	101 (41.6)	39 (42.4)
Malignancy[b]	283 (42.5)	18 (31.6)	119 (43.4)	115 (47.3)	31 (33.7)
Hyperlipidemia	87 (13.1)	4 (7.0)	26 (9.5)	38 (15.6)	19 (20.7)[a]
Hypertension	335 (50.3)	6 (10.5)	107 (39.1)	147 (60.5)	75 (81.5)[a]
Cardiovascular disease	189 (28.4)	16 (28.1)	71 (25.9)	68 (28.0)	34 (37.0)
Renal disease	186 (27.9)	11 (19.3)	79 (28.8)	72 (29.6)	24 (26.1)
Neurological disease	184 (27.6)	11 (19.3)	67 (24.4)	81 (33.3)	25 (27.2)
Pulmonary disease	71 (10.7)	1 (1.8)	23 (8.4)	41 (16.9)[a]	6 (6.5)
Hepatobiliary disease	110 (16.5)	3 (5.3)	54 (19.7)	39 (16.0)	14 (15.2)
Autoimmune disease	152 (22.8)	12 (21.1)	62 (22.6)	57 (23.5)	21 (22.1)
Prior surgery within three months	123 (18.5)	6 (10.5)	53 (19.3)	46 (18.9)	18 (19.6)
Clinical manifestations					
Bacteremia	548 (82.3)	35 (61.4)[a]	216 (78.8)	206 (84.8)	91 (98.9)[a]
Sepsis	238 (35.7)	12 (21.1)	113 (41.2)	83 (34.2)	30 (32.6)
Septic shock	56 (8.4)	4 (7.0)	26 (9.5)	17 (7.0)	9 (9.8)
Final outcomes					
Mortality within one month	33 (5.0)	0 (0)	10 (3.6)	13 (5.3)	10 (10.9)[a]
Mortality within one year	82 (12.3)	1 (1.8)	34 (12.4)	27 (11.1)	20 (21.7)[a]

All data are expressed as numbers and percentages for categorical data and median (IQR) for continuous data.
[a] a *P* value < 0.05 is marked. The p values are the comparisons of results among the groups of cases in patients aged 18–39 years, 40–64 years, 65–84 years, and ≥85 years old.
[b] Malignancy includes Hodgkin and non-Hodgkin lymphomas, leukemia and solid organ tumor.
[c] One case of postpartum endometritis was enrolled.

Table 2
Capsular serotype distribution of Group B streptococcus (GBS) infections in nonpregnant adults from CGMH, 2014–2020.

Capsular serotypes	Ia	Ib	II	III	V	VI	Others[a]
Bacteremia without other focus	104 (80.6 %)	47 (73.4 %)	51 (82.3 %)	85 (85.0 %)	59 (86.8 %)	170 (77.3 %)	19 (82.6 %)
Osteoarticular infection	6 (4.7 %)	3 (4.7 %)	6 (9.7 %)	4 (4.0 %)	3 (4.4 %)	8 (3.6 %)	1 (4.3 %)
Skin and soft tissue infection	10 (7.8 %)	7 (10.9 %)	4 (6.5 %)	4 (4.0 %)	4 (5.9 %)	33 (15.0 %)	1 (4.3 %)
Intra-abdominal infection	1 (0.8 %)	2 (3.1 %)	1 (1.6 %)	5 (5.0 %)	0 (0)	4 (1.8 %)	1 (4.3 %)
Pneumonia	5 (3.9 %)	1 (1.6 %)	0 (0)	2 (2.0 %)	0 (0)	1 (0.5 %)	1 (4.3 %)
Urinary tract infection	1 (0.8 %)	2 (3.1 %)	0 (0)	0 (0)	1 (1.5 %)	1 (0.5 %)	0 (0)
Meningitis	1 (0.8 %)	2 (3.1 %)	0 (0)	0 (0)	1 (1.5 %)	1 (0.5 %)	0 (0)
Endocarditis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.9 %)	0 (0)
Others[b]	1 (0.8 %)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total	129 (19.4 %)	64 (9.6 %)	62 (9.3 %)	100 (15.0 %)	68 (10.2 %)	220 (33.0 %)	23 (3.5 %)

All data are expressed as numbers and percentages.
[a] Including serotype IV (n = 7), VII (n = 2), VIII (n = 2), IX (n = 4), and nontypable (n = 8) isolates.
[b] One case of postpartum endometritis was enrolled.

between the sexes (data not shown). Although bacteremia without focus was the most common clinical feature, patients aged 19–39 years had a significantly increased rate of non-bloodstream infections (24.6 %, $p < 0.001$). The most common clinical manifestation was bacteremia, and 35.7 % of patients had GBS sepsis, and 8.4 % of patients had septic shock. Almost all the older patients aged ≥85 years (98.9 %) experienced bacteremia during the course of hospitalization.

Ampicillin or penicillin was the major treatment for these patients (91.4 %, n = 609); only 4.8 % (n = 32) of patients received vancomycin, and the rest were treated with tetracycline, fluoroquinolones, or macrolides. The mortality rates of the cohort were 5.0 % (total n = 33 deaths) and 12.3 % (total n = 82 deaths) within one month and one year after the onset of invasive GBS diseases, respectively. The mortality rates were comparable between male and female patients (4.7 % [15/321] vs.

5.2 % [18/345], p = 0.856) but were significantly greater in older patients (Table 1). Except for two patients who died within one month due to intra-abdominal infections, all other instances of mortality (n = 31) were in cases of bacteremia without other foci.

3.2. Molecular epidemiology of GBS isolates

Type VI was the most common serotype of the GBS isolates (33.8 %), followed by types Ia (19.4 %), III (15.0 %), V (10.2 %), Ib (9.6 %), and II (9.3 %). The GBS serotypes did not vary significantly according to patient sex or age group. However, there was an increasing trend in type Ia GBS isolates along with decreasing trends in type VI and type V GBS isolates as causes of adult invasive infections during the study period (Fig. 1). The MLST results of a representative sample of 482 GBS isolates (72.4 % of the cases) are summarized in Table 3. The GBS isolates were mainly distributed among the six major CCs—namely, CC-1, CC-12, CC-17, CC-19, CC-23 and CC-452. The CCs were not strongly correlated with the capsular serotype, as described in previous studies (Table 4), and they were also not strongly correlated with clinical features or patient demographics, including age, sex and underlying chronic comorbidities. The CC1 GBS isolates accounted for the most common cause of invasive GBS infections (n = 240, 49.8 %) and included serotypes Ib, II, III, V, and VI. The CC12 strain was exclusively type Ib (n = 46, 9.5 %), and the CC17 and CC19 GBS isolates were type III.

3.3. Antibiotic susceptibility

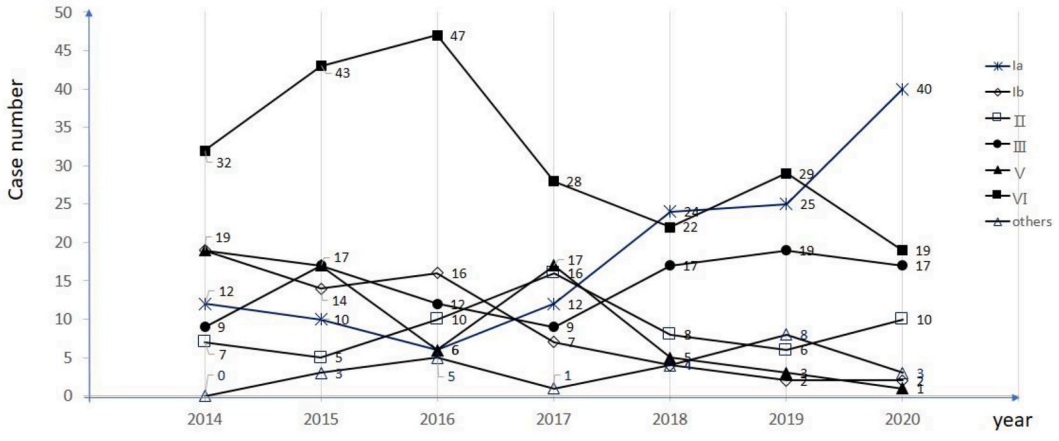
All GBS isolates from adults with invasive infections were susceptible to penicillin, ampicillin, vancomycin and cefotaxime. High resistance rates of 42.6 % (284/666) and 39.2 % (261/666) to erythromycin and clindamycin, respectively, were noted in the GBS isolates. The trend of resistance to erythromycin and clindamycin was stable throughout the study period (data not shown). The antibiotic resistance profiles of GBS isolates were not significantly different between different patient sexes or age groups or among GBS isolates from different sources. Because almost all patients were treated with penicillin or ampicillin, to which all GBS isolates were susceptible, none of the patients in the cohort had a delay in treatment or received inappropriate antibiotics. Therefore, the treatment outcomes were not associated with the antibiotic resistance profiles of the GBS isolates.

Particularly high resistance rates to erythromycin and clindamycin were noted in type Ib (87.5 %), type V GBS (67.6 %) and type III (55.0–59.0 %) GBS isolates (all p values < 0.05 compared with the other GBS serotypes). Because there was a high correlation only between serotype Ib and sequence type (ST)-12, the antibiotic resistance rates to erythromycin and clindamycin were also high in the CC12 (96.4 %) GBS isolates. Additionally, most of the GBS isolates (91.9 %, 261/284) that were resistant to erythromycin were also resistant to clindamycin.

4. Discussion

We found that adults with invasive GBS had the following characteristics: advanced age, multiple chronic comorbidities, and mainly bacteremia without other foci. Type VI, type Ia and type III accounted for more than two-thirds of all GBS isolates associated with adult invasive infections and were distributed mainly in CC1, CC12 and CC17. Although type VI was the most common in our cohort (33.0 %), type VI/CC1 is an uncommon serotype and rarely accounts for more than one-fifth of adult GBS invasive infections in the literature.[7–16] In the cohort, most patients responded to first-line antibiotic treatment, and the mortality rate of our patients was comparable to that reported in previous studies. Because underlying infections and extremely old age presumably account for most cases of mortality, the independent risk factors for treatment failure and final mortality were not investigated in this study.

The distribution of serotypes in GBS isolates from adults with invasive infections varies greatly across different geographic areas over time.[7–16] While type V GBS isolates are the most common in the United States, type Ib, type III and type V GBS isolates are predominant in some European and Asian countries.[9–11,13] In our cohort, types Ia, Ib, II, III, V and VI accounted for 96.5 % of all the isolates. Interestingly, type VI GBS isolates were reported to account for less than 2–4 % of the total in other countries[7–16] but accounted for 33.0 % of our GBS isolates. Some studies from Asian countries reported that type VI GBS isolates account for approximately 10–12 % of adult invasive diseases.[27,28] In contrast to the significant predominance of hypervirulent CC-17 as a cause of neonatal sepsis and meningitis worldwide, CC-17 GBS strains accounted for only 3.5 % of adult patients in the present cohort.[20,24] Additionally, the CC1



	2014	2015	2016	2017	2018	2019	2020
Ia	12	10	6	12	24	25	40
Ib	19	14	16	7	4	2	2
II	7	5	10	16	8	6	10
III	9	17	12	9	17	19	17
V	19	17	6	17	5	3	1
VI	32	43	47	28	22	29	19
others	0	3	5	1	4	8	3
Total	98	109	102	90	84	92	92

Fig. 1. Number of invasive GBS cases in adults caused by different serotypes each for each year from 2014 to 2020.

Table 3
The MLST results of adults with Group B Streptococcus (GBS) invasive diseases from Chang Gung Memorial Hospital (CGMH), 2014–2018.

	CC1	CC12	CC17	CC19	CC23	CC452	Others[a]
Bacteremia without other focus	214 (78.1 %)	46 (75.4 %)	13 (76.5 %)	32 (82.1 %)	23 (79.3 %)	35 (79.5 %)	16 (88.9 %)
Osteoarticular infection	11 (4.0 %)	3 (4.9 %)	2 (11.8 %)	2 (5.1 %)	2 (6.9 %)	4 (9.1 %)	0 (0)
Skin and soft tissue infection	39 (14.2 %)	6 (9.8 %)	2 (11.8 %)	2 (5.1 %)	2 (6.9 %)	5 (11.4 %)	1 (0.6 %)
Intra-abdominal infection	4 (1.5 %)	1 (1.6 %)	0 (0)	2 (5.1 %)	0 (0)	0 (0)	0 (0)
Pneumonia	1 (0.4 %)	1 (1.6 %)	0 (0)	1 (2.6 %)	1 (3.4 %)	0 (0)	0 (0)
Urinary tract infection	1 (0.4 %)	2 (3.3 %)	0 (0)	0 (0)	1 (3.4 %)	0 (0)	0 (0)
Meningitis	3 (1.1 %)	2 (3.3 %)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Endocarditis	1 (0.4 %)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Others[b]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.6 %)
Total	274 (56.8 %)	61 (12.7 %)	17 (3.5 %)	39 (8.1 %)	29 (6.0 %)	44 (9.1 %)	18 (3.7 %)

All the data are expressed as numbers and percentages.
[a] Including CC26 (n = 1, 0.2 %), CC327 (n = 5, 1.0 %), and CC459 (n = 3, 0.6 %).
[b] One case of postpartum endometritis was enrolled.

GBS isolates in our cohort included types Ib, II, III, V, and VI, in contrast to previous studies showing that serotype is often highly correlated with sequence type and that most CC1 GBS isolates are type V or type VI.[11,12,27,28]

In our cohort, the 30-day mortality rate and all-cause mortality rate within one year were comparable with those reported in studies from other countries, including some multicenter and population-based studies, which reported mortality rates ranging between 6.8 % and 12.5 %.[4–6,8,10] The patient demographics in our cohort were basically comparable to those in other studies in which elderly individuals, patients with chronic comorbidities, and bacteremia without focus constituted the majority of patients with invasive GBS diseases.[4–6,8,14] Overall, 80.3 % of our patients had bacteremia without focus, which was significantly higher than the rates reported in previous studies.[7–16] We found that younger patients had a significantly higher rate of non-bloodstream GBS infections; no such finding has been mentioned in previous studies.[7–16] There were significantly fewer cases of GBS meningitis and soft tissue infections in our cohort.[4–6,8,14] Vuillemin et al. reported that approximately 5 % of adults with invasive GBS infections had central nervous system infections, and another 5 % had endocarditis, which may be associated with a worse outcome.[14] A higher percentage of septic-shock-associated GBS infections was also noted in two European studies.[4,8] We suspected that type VI GBS isolates may be associated with lower virulence, and a relatively low mortality rate was noted in our cohort. However, most studies have not reported a significant association between serotypes and outcomes in adults with invasive GBS diseases.[7–16]

In our cohort, we detected a moderate percentage of GBS isolates that were resistant to macrolides and clindamycin, which was significantly lower than the corresponding resistance rates among collected isolates that caused neonatal sepsis during the contemporary period.[20,22] However, as with the GBS isolates from neonatal sepsis patients, especially high antibiotic resistance rates were noted for type III, type Ib, and type V strains.[29] The overall resistance rate in our cohort was comparable to the 26.3–48 % resistance rates reported in previous studies.[14,15,17,30] Although the emergence of multidrug-resistant GBS isolates has been reported in several recent studies,[17,20,27,30] multidrug resistance is rarely noted in clinical GBS isolates in Taiwan. Most of our patients received ampicillin or penicillin as first-line therapy, and vancomycin was administered to only a few patients who were allergic to penicillin and did not respond to second-line antibiotics. Our data were consistent with those of previous studies in that the treatment outcomes were not significantly different between antibiotic-susceptible and antibiotic-resistant GBS strains.[12,14,30] As in most studies in Taiwan, none of our GBS isolates were resistant to fluoroquinolones or tetracycline.[31–33]

This study had several limitations. This was a single-center study from Taiwan, and the results may be poorly generalizable to other geographical areas. Therefore, the distributions of GBS serotypes, STs or CCs, clinical features and patient demographics are not close to those described in other countries. We suggest that a nationwide cohort study or at least multicenter studies are necessary to reflect the epidemiology of invasive GBS infections in adults. We could not find trends or changes over a 7-year study period in this study, and the therapeutic strategies may have changed. Additionally, MLST analysis was not performed for all the GBS isolates, and the incidence rates, risk factors, and predictors of mortality could not be investigated in this study.[34,35]

In conclusion, although most invasive GBS infections in adults are curable, they are an increasing burden with a considerable rate of mortality, mostly due to advanced age and underlying chronic comorbidities. The clinical features and molecular characteristics of GBS isolates are diverse. Although resistance to β-lactams is low in clinical GBS isolates, high rates of resistance to erythromycin and clindamycin in some GBS serotypes should be a concern. There have been recent reports of GBS meningitis in older people, as well as complicated GBS sepsis, highlighting the importance of continued surveillance and the development of vaccines to prevent GBS infections in the future.

Abbreviations

CSF: cerebrospinal fluid; CDC: Centers for Disease Control and Prevention; CI: confidence interval; CC: clonal complex; CGMH: Chang Gung Memorial Hospital; EOD: early-onset disease; GBS: Group B Streptococcus; IAP: intrapartum antibiotic prophylaxis; LOD: late-onset disease; MLST: multilocus sequence typing; ST: sequence type; OR: odds ratio; PCR: polymerase chain reaction; TPN: total parenteral nutrition; VAP: ventilator-associated pneumonia.

CRediT authorship contribution statement

Jen-Fu Hsu: Writing – original draft, Resources, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Wei-Ju Lee:** Software, Methodology, Investigation, Data curation. **Shih-Ming Chu:** Resources, Project administration, Methodology, Formal analysis, Data curation. **Yao-Sheng Wang:** Methodology, Investigation, Formal analysis, Data curation. **Hsuan-Rong Huang:** Resources, Methodology, Investigation, Formal analysis. **Peng-Hong Yang:** Project administration, Investigation, Formal analysis, Data curation. **Jang-Jih Lu:** Writing – review & editing, Validation, Supervision, Software, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Ming-Horng Tsai:** Writing – review & editing, Writing – original draft, Validation, Investigation, Formal analysis, Data curation, Conceptualization.

Availability of data and materials

The datasets used/or analyzed during the current study are available from the corresponding author upon reasonable request.

Table 4
Relationships between sequence types, clonal complexes, and serotypes of 482 *Streptococcus agalactiae* isolates causing adult invasive diseases in CGMH, 2014 to 2020.

Serotype	N (%) (total 482)	CC	ST	N (%)	Bacteremia without focus [n (%)]	Mortality [n (%)]
Ia	64 (13.3 %)	CC23	ST23	23 (35.9 %)	19 (82.6 %)	2 (8.7 %)
		CC452	ST24	9 (14.1 %)	9 (100 %)	1 (11.1 %)
			ST 890	7 (10.9 %)	3 (42.9 %)	
		others		15 (23.4 %)	12 (80.0 %)	
Ib	65 (13.5 %)	CC1	ST1	10 (15.4 %)	7 (70.0 %)	
		CC12	ST12	46 (70.8 %)	34 (73.9 %)	
		others		9 (13.8 %)	9 (100 %)	1 (11.1 %)
II	46 (9.5 %)	CC1	ST1	31 (67.4 %)	24 (77.4 %)	1 (3.2 %)
			ST3	6 (13.0 %)	5 (83.3 %)	
		others		9 (19.6 %)	8 (88.9 %)	
III	64 (13.3 %)	CC1	ST1	7 (10.9 %)	4 (57.1 %)	
		CC17	ST17	15 (23.4 %)	12 (80.0 %)	1 (6.7 %)
		CC19	ST19	22 (34.4 %)	17 (77.3 %)	
			ST335	7 (10.9 %)	7 (100 %)	
		others		13 (20.3 %)	10 (76.9 %)	1 (7.7 %)
V	59 (12.2 %)	CC1	ST1	26 (44.1 %)	22 (84.6 %)	
		CC1	Others	2 (3.4 %)		
		CC452	ST890	15 (25.4 %)	11 (73.3 %)	1 (6.7 %)
			ST24	7 (11.9 %)	6 (85.7 %)	
		Others		9 (15.3 %)		
VI	172 (35.7 %)	CC1	ST1	162 (94.2 %)	122 (75.3 %)	6 (3.7 %)
			ST920	4 (2.3 %)	3 (75.0 %)	
		others		6 (3.5 %)	4 (66.7 %)	
Others[a]	10 (2.1 %)			10 (100 %)	10 (100 %)	1 (10.0 %)

CC: clonal complex, ST: sequence type; UN: unknown.
[a] Including type IV (n = 5), type VII (n = 2), type VIII (n = 1), and nontypable (n = 2).

Ethics approval statement and consent to participate

This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital, with a waiver of informed consent because all patient records and information were anonymized and deidentified prior to analysis.

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Declaration of competing interest

All authors declared no conflict of interest.

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