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Article

Community-acquired group B streptococcal meningitis in adults: 33 cases from prospective cohort studies

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SUMMARY

Objectives: *Streptococcus agalactiae* (group B streptococcus, GBS) is an uncommon cause of bacterial meningitis in adults. We describe clinical characteristics, serotype distribution and outcome of adult GBS meningitis.

Patients and methods: Patients aged 16 years or older with GBS cultured in cerebrospinal fluid included in two prospective nationwide cohort studies performed in the Netherlands between 1998–2002 and 2006–2017 were evaluated.

Results: We identified 33 patients with GBS meningitis with a median age of 58 years of whom 22 were male (67%). The mean annual incidence was .16 per 1.000.000 adults. Ten patients (30%) had an immunocompromised state, which was due to alcoholism in 6 (18%) and diabetes mellitus in 4 (12%). Eleven patients (33%) had a distant focus of infection of whom 4 had endocarditis (13%). Seven patients (21%) died and 6 (18%) survivors had sequelae causing disability, including reduced vision and blindness due to endophthalmitis ($n = 2$). Twenty patients (61%) made a full recovery. Most common bacterial serotypes were serotype III (41%) and Ia (25%). Serotype V was associated with increased mortality (3 of 4 [75%] serotype V died vs. 4 of 28 [14%] other serotypes, $P = .025$).

Conclusion: GBS is a rare cause of meningitis in adults that more frequently occurs in patients with underlying comorbidities. Patients should be carefully evaluated for distant foci of infection. GBS serotype V is associated with poor outcome.

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Introduction

Bacterial meningitis is a severe infection with substantial mortality and morbidity.[1,2] Most common pathogens are *Streptococcus pneumoniae* and *Neisseria meningitidis*.[3] In neonates *Streptococcus agalactiae* (group B streptococci; GBS) cause the majority of cases.[4] Cohort studies of adults with bacterial meningitis showed that .4–7.4% of all cases of meningitis in adults were due to GBS but prospective clinical data is lacking.[5–7] Few studies, mainly case reports or small cases series, have addressed GBS meningitis in adults.[8,9] In this study, we describe the clinical features, complications, outcome, and bacterial serotype distribution of adult GBS meningitis from 2 nationwide surveillance studies in the Netherlands.

Methods

We included all patients aged ≥16 years with a community-acquired bacterial meningitis in the Dutch Meningitis Cohort study from October 1998 to April 2002 (cohort 1) and the MeninGene study from April 2006 to April 2017 (cohort 2). Methods have been described previously.[1,10] In summary, patients in these nationwide cohorts were identified through the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM), which receives cerebrospinal fluid (CSF) and blood isolates from approximately 85% of all patients with bacterial meningitis in the Netherlands.[11,12] From this cohort, we selected all patients with a CSF culture positive for GBS. The incidence is calculated as the number of episodes of GBS meningitis per 1.000.000 adults (≥16 years old) per year. Episodes of hospital-acquired meningitis (defined as bacterial meningitis

Abbreviations: CSF, cerebrospinal fluid; GBS, Streptococcus agalactiae, group B streptococci; GCS, Glasgow Coma Scale; NRLBM, The Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM).

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that occurred while in hospital or within 1 week after discharge), patients with severe head trauma or neurosurgery in the previous month, and patients with a neurosurgical device were excluded.

Written information about the study was given to the patients or their legal representatives and informed consent for participation was asked. Case-record forms were used to collect data on medical history, symptoms and signs on admission, laboratory findings at admission, clinical course, outcome and treatment. Patients with an immunoproliferative disorder, an immunodeficiency disease, diabetes mellitus, alcoholism, liver cirrhosis, asplenia, HIV infection or receiving immunosuppressive drugs were considered to be immunocompromised. Outcome was scored by the Glasgow Outcome Scale score.[13] Where a score of 1 indicates death, a score of 2 is vegetative state (unable to interact with the environment), a score of 3 is severe disability (unable to live independently but can follow commands), a score of 4 is moderate disability (capable of living independently but unable to return to work or school), and a score of 5 is mild or no disability (able to return to work or school). A favourable outcome was defined as a score of 5, and an unfavourable outcome as a score of 1–4.

Serotyping of GBS was done by the NRLBM with a latex agglutination test as previously described.[14] Genotyping of all bacterial isolates was performed by the NRLBM in collaboration with the Wellcome Trust Sanger Institute, where GBS isolates were grouped into clonal complexes (CC) by multilocus sequence typing (MLST) based on the basis of similarities in seven housekeeping genes, according to the GBS MLST database (http://pubmlst.org/sagalactiae) and with use of the Cluster eBURST software program.[15,16] If serotype data based on latex agglutination was not available we used serotype data based on genotyping.

For statistical analysis we used the Fishers exact and Mann–Whitney U tests. Statistical tests were two-sided and a *p*-value below .05 was considered to denote statistical significance. The study was approved by the medical ethic committee of the Academic Medical Centre, Amsterdam, the Netherlands.

Results

A total of 2579 episodes of CSF culture positive community acquired bacterial meningitis were included; 696 from 1998 to 2002, and 1883 from 2006 to 2017. Thirty-three of these 2579 episodes (1.3%) were caused by GBS. Annual incidence per year ranged from 0 in 2000 and 2006 and .37 in 2009. The mean annual incidence rate during the first cohort (1998–2002) was .08 per 1.000.000 adults and .18 during the second cohort (2006–2016).[17]

The 33 episodes occurred in 33 patients with a median age of 58 years (IQR 49-69) and 22 (67%) were male (Table 1). No episodes occurred in pregnant or puerperal women. Of the 33 patients, 10 (30%) had an immunocompromised status, which was due to alcoholism in 6 (18%) and diabetes mellitus in 4 (12%). Five of 23 (22%) immunocompetent patients had other risk factors for meningitis, including 2 patients with active CSF leakage, a medical history of a skull base fracture in 1 with possible CSF leakage, recurrent meningitis with erosive lesions of the cranium on CT in 1 and history of craniotomy in 1. Eighteen patients (55%) were healthy adults without predisposing factors. A focus of infection outside the central nervous system was found in 11 (33%) patients and consisted of endocarditis in 4 (13%), otitis or sinusitis in 4 (12%) and dental infection in 3 (10%). All of the patients with endocarditis had blood cultures positive for GBS, were treated with prolonged intravenous antibiotics during 6 weeks or until death. The involved valves in these patients were the aortic valve in 2, the mitral valve in 1 and both aortic and mitral in 1. Two of the four patients with endocarditis died, the other two had unfavourable outcomes due to blindness after endophthalmitis in 1 and focal neurological deficits after cerebral infarction in the other.

The most common symptoms on presentation were headache, fever and neck stiffness, which were found in 21 (70%), 23 (79%) and 21 (70%) patients. An altered mental state defined a Glasgow Coma Scale (GCS) score <14 was present in 23 patients (70%). Twelve (38%) of the patients presented with the classic meningitis triad of fever, neck stiffness and altered mental state. Focal neurological deficits, defined as aphasia, cranial nerve palsy, monoparesis or hemiparesis, were present in 3 of 32 patients (9%).

Twenty-four of 33 patients (73%) had at least one individual CSF predictor of bacterial meningitis defined by as a CSF glucose concentration <1.9 mmol/L, CSF glucose:blood glucose ratio <.23, protein level >2200 mg/L, leukocyte count >2000 cells/μL, or >1180 polymorphonuclear leucocytes/μL.[18] Gram staining of CSF was positive in 17 patients (61%) of 28 patients and showed gram-positive cocci in all. In 24 of 31 patients (77%) blood cultures were positive for GBS. Cranial CT was performed in 24 patients (73%) and showed new abnormalities in 5 patients, including cerebral infarction in 3, and generalized oedema and focal cerebritis in 1 each.

During admission neurological complications occurred in 17 of the 33 patients (52%), consisting of focal neurological deficits in 11 (33%), a decreased consciousness in 10 (30%) and seizures in 1 (3%) (Table 2). In 5 patients, abnormalities were identified on cranial CT or MRI during admission consisting of cerebral infarction in 3, a lamina cribrosa defect in 1, and cerebritis in 1 patient. Cardiorespiratory failure occurred in 12 of 33 patients (36%) of whom 10 (30%) were mechanically ventilated.

Fourteen patients had an unfavourable outcome (42%), of whom 7 patients (21%) died, with a median time from admission to death of seven days (range 0–21 days). Two patients developed bilateral endophthalmitis during admission, which resulted in bilateral blindness in one and reduced vision in the other. Age above 65 years, immunocompromised state and endocarditis were associated with unfavourable outcome (Table 3). Characteristics associated with death were age of 65 years and older, immunocompromised state, alcoholism and state of coma (GCS < 8) at presentation (Table 3).

Serotype was based on latex agglutination in 5 (15%), genotyping in 2 (6%) and both in 25 (76%) isolates, for 1 isolate no data was available. The most common serotypes were serotype III, which was identified in 13 episodes (41%), serotype Ia in 8 (25%) and serotype V in 4 patients (13%; Fig. 1). The most common clonal complexes were CC17 and CC23 (both 8 times [25%]) followed by CC1 (5 times [16%]) and CC10 (3 times [9%]). Serotype V was associated with mortality (3 of 7 [43%] vs. 1 of 25 [4%] other serotypes; $P = .025$).

Discussion

GBS is an uncommon cause of community-acquired bacterial meningitis in adults (1.3% of cases). It mainly occurs in patients with underlying comorbidities such as alcoholism, diabetes and distant foci of infections. We identified patients with endocarditis, endophthalmitis, and spondylodiscitis. These severe and normally uncommon coexisting conditions in bacterial meningitis need longer duration of IV antibiotics. Therefore, adults presenting with GBS meningitis should be carefully evaluated for distant infections.

Endocarditis was common in our case series (13%). A retrospective case-series and review of the literature found a similar proportion of 8%.[8] Endocarditis is an uncommon coexisting condition in bacterial meningitis due to other bacteria (2% of cases) but has been associated with a high rate of unfavourable outcome.[19,20] In a case series, clues leading to the diagnosis of endocarditis were cardiac murmurs, persistent or recurrent fever, a history of heart valve disease, and *Staphylococcus aureus* as the causative pathogen of bacterial meningitis.[19] Our study shows that clinicians should

Table 1
Demographic and clinical characteristics.

Characteristics	*n*/*N* (%)	Characteristics	*n*/*N* (%)
Age (years)	58 (49–69)	Neck stiffness	22/31 (70%)
Men	22/33 (67%)	Body temperature (°C)[b]	38.7 (37.3–39.8)
History of meningitis	4/33 (12%)	Fever (≥38 °C)	21/33 (64%)
Symptoms < 24 h	15/33 (46%)	Score on Glasgow Coma Scale[b]	11 (10–15)
Seizures	3/33 (9%)	<14 altered mental status	23/33 (70%)
Pretreatment with antibiotics	3/33 (9%)	<8 coma	3/33 (9%)
CSF leak	3/33 (9%)	Triad of fever, neck stiffness and altered mental status	12/32 (38%)
Immunocompromised status	10/33 (30%)	Focal neurologic deficits [f]	3/32 (9%)
Immunosuppressive drugs	1/33 (3%)	Laboratory findings on presentation[c]	
Diabetes Mellitus	4/33 (12%)	Blood tests	
Alcoholism	6/33 (18%)	Positive blood culture	24/31 (77%)
Foci of infection	11/33 (33%)	C-reactive protein (mg/L)[d]	68 (17–233)
Endocarditis	4/32 (13%)	Leukocyte count ($x10^9$/L)[b]	17.6 (8.0–22.4)
Otitis or sinusitis	3/33 (9%)	Thrombocyte count ($x10^9$/L)	156 (102–225)
Spondylodiscitis[a]	2/30 (7%)		
Odontogenic infection[a]	3/30 (10%)	CSF tests	
Pneumonia	1/32 (3%)	White cells count (cells per µL)[c]	1425 (458–7077)
Endophthalmitis[a]	1/30 (3%)	Protein (g/L) [d]	3.1 (1.9–5.8)
Symptoms and signs on presentation		Glucose (mmol/L) [d]	2.1 (1.2–3.7)
Headache	23/29 (79%)	CSF:Blood glucose ratio[e]	.25 (.09–.38)
Nausea	14/28 (50%)	Positive gram stain	17/28 (61%)
		Abnormalities cranial CT/MRI	10/25 (40%)

[a] Data available of cohort from 2006 to 2017.
[b] Data was known for 33 patients (100%).
[c] Data was known for 32 patients (97%).
[d] Data was known for 31 patients (94%).
[e] Data was known for 30 patients (91%).
[f] Cranial nerve palsy, aphasia, monoparesis, or hemiparesis.

be aware of the risk of endocarditis in patients with GBS meningitis and a cardiology consultation and echocardiogram should be performed in GBS meningitis patients to identify or rule out co-existing endocarditis.

Odontogenic infections, spondylodiscitis and endophthalmitis were also relatively common in adults with GBS meningitis. Endophthalmitis has previously been described as a complication of GBS septic arthritis, pharyngitis, cutaneous infections and pneumonia.[21] Early identification of endophthalmitis is important as there may be therapeutic consequences, such as intra-vitreous antibiotics treatment or vitrectomy.[22] The prognosis for visual outcome in GBS endophthalmitis often is poor despite adequate therapy.[21,22]

Previous case series found that between 11% and 14% of GBS meningitis episodes occurred in pregnant or puerperal women, in contrast to our current results in which no puerperal woman with GBS meningitis were identified.[8,9] This difference between the results of our prospective study and previous reports may be due to the implementation of GBS preventive guidelines in pregnancy, recommending intrapartum antibiotic prophylaxis to women with risk factors for perinatal GBS disease.[23] A recent systematic review found that the incidence of GBS sepsis in pregnant and puerperal women the US decreased after the implementation of preventive guidelines.[24]

One in five patients with GBS meningitis died and half had neurological sequelae. Risk factors for mortality previously identified were co-morbid conditions, older age and neurological or systemic complications, which we confirmed with our prospectively collected data.[8,9] We identified GBS serotype as predictor for mortality in bacterial meningitis. Patients infected with GBS serotype V had a ten-fold higher mortality rate. Confirmation of increased diseases severity by serotype V in other populations is needed as the number of patients in our study with serotype V was relatively small. A previous study on all types of invasive GBS disease in all age categories found serotype Ia to be associated with increased mortality compared to other serotypes (RR, 1.3; 95% CI, 1.1–1.6, overall mortality 7.9%).[25] In our bacterial meningitis patients, serotype Ia was not associated death.

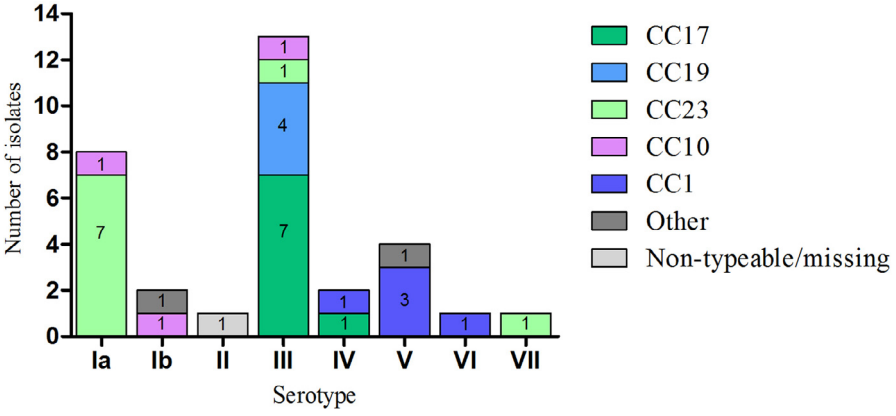

Fig. 1. Serotype and clonal complex distribution.

Table 2
Treatment and outcome.

Characteristics	*n*/*N* (%)
Treatment	
Adjuvant dexamethasone	25/30 (83%)
Per protocol[a]	24/30 (80%)
Neurological complications[b]	17/33 (52%)
Systemic complications	13/33 (39%)
Cardiorespiratory failure	12/33 (36%)
Mechanical ventilation	10/33 (10%)
Score on Glasgow Outcome Scale	
1 (death)	7/33 (21%)
2 (vegative state)	0/33 (0%)
3 (severe disability)	2/33 (6%)
4 (moderate disability)	4/33 (12%)
5 (mild or no disability)	20/33 (61%)
Sequelae	
Focal neurological deficits	11/33 (33%)
Endophthalmitis[c]	2/30 (7%)
Hearing loss[d]	4/26 (15%)

[a] Defined as 10 mg 4 times per day for 4 days.
[b] Defined as impairment of consciousness, seizures, focal neurological abnormalities.
[c] Data of patients from cohort 2006–2017.
[d] Data for patients who survived.

Table 3
Clinical characteristics on admission and outcome.

Characteristics	Favorable ($n=20$)	Unfavorable ($n=13$)	*P*-value
Age > 65 years	3/20 (15%)	7/13 (54%)	.026
Immunocompromised state	3/20 (15%)	7/13 (54%)	.026
Endocarditis	0/20 (0%)	4/12 (33%)	.014
Characteristics	Survival ($n=26$)	Death ($n=7$)	*P*-value
Age > 65 years	5/26 (19%)	5/7 (71%)	.016
Immunocompromised state	2/26 (8%)	5/7 (71%)	.016
Alcoholism	2/26 (8%)	4/7 (57%)	.011
Coma on admission	0/26 (0%)	3/7 (43%)	.006

A limitation of the study is that the incidence in our cohort is likely to be an underestimation of the actual incidence because we only included patients with positive CSF culture. Fifteen to 33% of patients that with string evidence of bacterial meningitis have negative CSF cultures.[2] Furthermore, the NRLBM receives isolates of approximately 85% of all patients with bacterial meningitis. However, there factors are unlikely to have led to a selection bias and affected the results.

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