

Outcome in patients with bacterial meningitis presenting with a minimal Glasgow Coma Scale score

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ABSTRACT

Objective: In bacterial meningitis, a decreased level of consciousness is predictive for unfavorable outcome, but the clinical features and outcome in patients presenting with a minimal score on the Glasgow Coma Scale are unknown.

Methods: We assessed the incidence, clinical characteristics, and outcome of patients with bacterial meningitis presenting with a minimal score on the Glasgow Coma Scale from a nationwide cohort study of adults with community-acquired bacterial meningitis in the Netherlands from 2006 to 2012.

Results: Thirty of 1,083 patients (3%) presented with a score of 3 on the Glasgow Coma Scale. In 22 of 30 patients (73%), the minimal Glasgow Coma Scale score could be explained by use of sedative medication or complications resulting from meningitis such as seizures, cerebral edema, and hydrocephalus. Systemic (86%) and neurologic (47%) complications occurred frequently, leading to a high proportion of patients with unfavorable outcome (77%). However, 12 of 30 patients (40%) survived and 7 patients (23%) had a good functional outcome, defined as a score of 5 on the Glasgow Outcome Scale. Patients presenting with a minimal Glasgow Coma Scale score on admission and bilaterally absent pupillary light responses, bilaterally absent corneal reflexes, or signs of septic shock on admission all died.

Conclusions: Patients with community-acquired bacterial meningitis rarely present with a minimal score on the Glasgow Coma Scale, but this condition is associated with high rates of morbidity and mortality. However, 1 out of 5 of these severely ill patients will make a full recovery, stressing the continued need for aggressive supportive care in these patients. *Neurol Neuroimmunol Neuroinflammation* 2014;1:e9; doi: 10.1212/NXI.000000000000009

GLOSSARY

ICP = intracranial pressure.

Bacterial meningitis is a serious and life-threatening disease.¹ *Streptococcus pneumoniae* and *Neisseria meningitidis* are the predominant causative pathogens of this disease in adults,² causing 80%–85% of all cases, with high associated morbidity and mortality rates.^{3–5} Many patients with bacterial meningitis present with an abnormal conscious state, and 15%–20% of patients are comatose upon presentation.⁵ An abnormal conscious state, in most studies graded by the Glasgow Coma Scale, is a strong predictor for poor disease outcome in bacterial meningitis.^{5,6} The exact cause of an abnormal conscious state in bacterial meningitis remains unclear, but it is likely caused by a complex interaction between severe brain inflammation, raised intracranial pressure (ICP), and resulting complications such as hydrocephalus, cerebral (micro)infarctions, or epileptic seizures.^{7–9} The evaluation of patients with an abnormal conscious state in bacterial meningitis might further be complicated by the use of antiepileptic or sedative medication.

The clinical features and outcome of the most severely ill patients, those who present with a score on the Glasgow Coma Scale of 3, are unknown. The time frame for concluding that neurologic

Supplemental data
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damage is irreversible in these patients is unclear. In this study we analyzed the incidence, clinical characteristics, complications, and outcome of patients with bacterial meningitis presenting with a minimal Glasgow Coma Scale score.

METHODS In a prospective nationwide observational cohort study in the Netherlands, we included episodes of community-acquired bacterial meningitis confirmed by culture of CSF in adults. Methods of the MeninGene Study have been described in detail elsewhere.^{5,10} In summary, all patients were 16 years of age or older and were listed in the database of the Netherlands Reference Laboratory for Bacterial Meningitis from January 2006 to March 2012. This laboratory receives CSF isolates from approximately 90% of all patients with bacterial meningitis in the Netherlands. Patients with negative CSF cultures, hospital-acquired meningitis, a neurosurgical device, or who underwent a neurosurgical operation within 1 month before bacterial meningitis onset were excluded. Patients using immunosuppressive drugs and those with asplenia, diabetes mellitus, alcoholism, or infection with immunodeficiency virus were considered immunocompromised. Informed consent was obtained from all participating patients or, in case of decreased consciousness, from their legally authorized representatives. Clinical data, including specific queries about the Glasgow Coma Scale score on admission, had been prospectively collected by means of an online case record form. The Glasgow Coma Scale grades coma severity according to 3 categories of responsiveness: eye opening, motor responses, and verbal responses, with scores ranging from 3 to 15.¹¹ Information about brainstem reflexes including pupillary light responses, respiratory drive, EEG data, intubation, and sedative medication at the time of presentation was not a standard part of the case record form. These data were all collected retrospectively by reanalyzing correspondence from ambulance and emergency departments.

At discharge, all patients underwent a neurologic examination performed by a neurologist, and outcome was graded according to the Glasgow Outcome Scale. This is a well-validated measurement scale with scores varying from 1 to 5.¹² A favorable outcome was defined as a score of 5 and an unfavorable outcome as a score of 1–4. Two clinicians independently classified the cause of death. The interrater agreement (κ) for cause of death was 0.73. Differences were resolved by discussion.

Standard protocol approvals, registrations, and patient consents. The study was approved by the ethics committee of the Academic Medical Center, Amsterdam, the Netherlands.

RESULTS From 2006 to 2012, 1,083 episodes of community-acquired bacterial meningitis were included in the cohort. Thirty of 1,083 patients (3%) presented with a Glasgow Coma Scale score of 3 on admission (figure 1). Fifteen patients (50%) were female and the median age was 65 years (interquartile range 49–76 years; table 1). Fifteen patients (50%) had one or more predisposing conditions for bacterial meningitis, consisting of otitis/sinusitis in 8, immunocompromised state in 6, and pneumonia in 2.

Data on pupillary light responses could be retrieved for 25 of 30 patients (83%). Pupillary light responses were bilaterally present in 15 patients (60%), unilaterally absent in 2 (8%), and bilaterally absent in 8 (32%; table 1). Anisocoria was noted in 6 of 20 patients (30%). Data on corneal reflexes could be retrieved for 9 patients, and corneal reflexes were bilaterally absent in 7 (including 4 patients with bilaterally absent pupillary light responses), unilaterally absent in 1, and bilaterally present in 1. One patient had an absent respiratory drive at time of presentation and died the next day. Of 30 patients, 13 (43%) were intubated prior to neurologic examination; 5 of these 13 patients (39%) received sedative drugs, 2 of whom also received muscle relaxant drugs. The remaining patients did not receive sedative medication prior to initial neurologic examination. Eight of 23 patients (35%) with a minimal Glasgow Coma Scale score presented with neck stiffness, 10 of 30 patients (33%) presented with seizures, and 9 of 26 patients (34%) had signs of septic shock at time of presentation.

Seizures consisted of tonic-clonic seizures in all 10 patients; 4 patients received benzodiazepines to stop the seizures and 1 patient received sedative drugs and muscle relaxant drugs prior to intubation. One patient had prolonged seizures despite benzodiazepines; it is unknown how the prolonged seizures were treated in this patient.

Cranial CT on admission was performed in 27 of 30 patients (90%) and was abnormal in 67% (table 1; figure 2). In 22 of 30 patients (73%), the minimal Glasgow Coma Scale score could be explained either by complications resulting from the meningitis (seizures in 10, hydrocephalus in 5, and cerebral edema in 7) or by sedative medication (5 patients). In the other 8

Figure 1 Distribution of scores on Glasgow Coma Scale for adults presenting with community-acquired bacterial meningitis

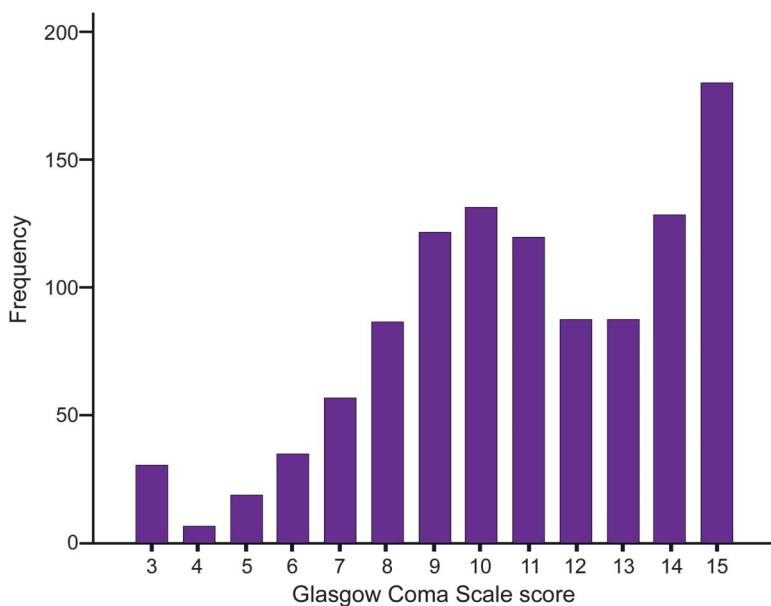


Table 1 Clinical characteristics of 30 patients with bacterial meningitis presenting with a minimal coma score^a

Characteristics	n/N (%) or median (IQR)
Age, y	65 (49–76)
Female	15/30 (50)
Predisposing conditions	15/30 (50)
Otitis/sinusitis	8/30 (27)
Immunocompromised state	6/30 (20)
Pneumonia	2/24 (8)
Duration of symptoms >24 h	14/26 (54)
Symptoms and signs on admission	
Bilaterally absent pupillary light reflex	8/25 (32)
Bilaterally absent corneal reflex	7/9 (78)
Temperature ≥38°C	21/29 (70)
Neck stiffness	8/23 (35)
Seizures	10/30 (34)
Systolic blood pressure, mm Hg ^a	130 (120–159)
Heart rate, beats/min ^a	102 (98–140)
Signs of septic shock ^b	9/26 (35)
Abnormal cranial CT	18/27 (67)
Generalized edema	8/27 (30)
Hydrocephalus	5/27 (19)
Presumed recent infarction	1/27 (4)
Subdural empyema/effusion	2/27 (7)
Mastoid opacification	7/27 (26)
Sinus opacification	4/27 (15)
Blood chemistry tests ^c	
Leukocyte count, cells/mm ³	15 (10–20)
ESR, mm/h	12 (5–60)
C-reactive protein, mg/L	221 (110–327)
Indexes of inflammation in the CSF ^d	
Leukocyte count, cells/mm ³	2,240 (160–10,750)
Leukocytes <1,000 cells/mm ³	10/27 (37)
Protein	5.5 (3.3–7.2)
CSF: blood glucose ratio	0.01 (0–0.13)
CSF culture	
<i>Streptococcus pneumoniae</i>	26/30 (87)
Adjunctive dexamethasone	25/29 (86)

Abbreviations: ESR = erythrocyte sedimentation rate; IQR = interquartile range.

^aSystolic blood pressure and heart rate were determined in 27 patients.

^bDefined as diastolic blood pressure <60 mm Hg, systolic blood pressure ≤90 mm Hg, or heart rate ≥120 beats/min.

^cLeukocyte count was determined in 30 patients, ESR in 9 patients, and C-reactive protein levels in 30 patients.

^dCSF leukocyte count was determined in 27 patients, CSF protein levels in 28 patients, and CSF: blood glucose ratio in 29 patients.

patients, the minimal score on the Glasgow Coma Scale was explained by a direct effect of the meningitis (defined as a combination of severe brain inflammation and raised ICP).

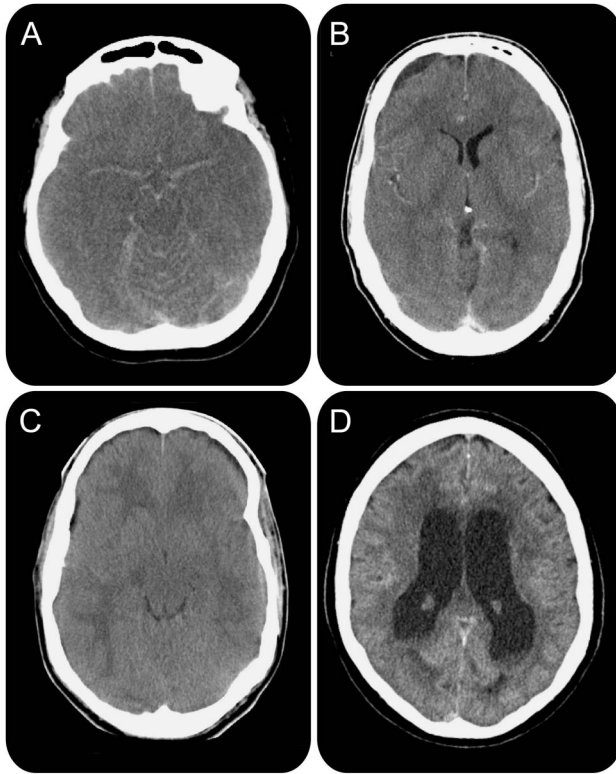
Cranial imaging was repeated during admission in 16 patients (all patients underwent CT scan, 1 patient underwent CT and MRI scan) and was abnormal in 10 patients (63%). New abnormalities not present on admission were found in 2 patients and consisted of cerebral infarctions in both.

Twenty-nine of the 30 patients (97%) had at least one individual CSF finding predictive of bacterial meningitis (glucose level <34 mg/dL [1.9 mmol/L], ratio of CSF glucose to blood glucose <0.23, protein level >220 mg/dL, or leukocyte count >2,000/mm³).¹³ Ten of 27 patients (37%) had a CSF leukocyte count below 1,000 cells/mm³, which has previously been associated with poor outcome.⁵ CSF cultures grew *S pneumoniae* in 26 patients (87%) and *Haemophilus influenzae*, *Salmonella enterica*, *Streptococcus pyogenes*, and *Staphylococcus aureus* in 1 patient each. Initial antibiotic treatment was microbiologically adequate in all patients and 25 of 29 patients (86%) received adjunctive dexamethasone on admission.¹⁴ The clinical characteristics, results of cranial imaging, and CSF analysis were similar when considering only patients who did not receive sedative medication (table e-1 at Neurology.org/nn).

The majority of patients (87%; table 2) developed complications during the clinical course. Systemic complications consisted of respiratory failure (15 of 25 [60%]), pneumonia (6 of 26 [23%]), and hyponatremia (4 of 27 [15%]). Neurologic complications consisted of seizures (7 of 30 [23%]), hearing impairment (4 of 30 [13%]), cerebral infarction (3 of 30 [10%]), and subdural empyema (2 of 30 [7%]). EEG was performed in 5 patients during the clinical course. Four of these patients had an isoelectric EEG (1 to 3 days after admission) and treatment was withdrawn resulting in immediate death. In 1 patient, the EEG was performed on the eleventh day showing severe cortical dysfunction (with some residual cerebral activity). Care was withdrawn and the patient subsequently died of multiorgan failure. One patient with hydrocephalus was treated with external ventricular drainage on the day of admission but died 3 days later. Four patients with hydrocephalus were not treated with external ventricular drainage because of other poor prognostic factors (multiorgan failure, clinically brain dead) or because the hydrocephalus was mild and spontaneously resolved on follow-up imaging. None of the patients were treated with continuous ICP measuring and ICP-directed treatment.

Twelve of the 30 patients (40%) survived and 7 patients (23%) had a good functional outcome, defined as a score of 5 on the Glasgow Outcome Scale. Neurologic sequelae were present on discharge in 5 of 12 survivors (42%) and consisted of cognitive impairment in 4, poor general condition in 2, and bilateral hearing loss and hemiparesis in 1 patient each; 3 surviving patients with sequelae were scored as moderately disabled on

Figure 2 Spectrum of abnormal CT scanning of patients with bacterial meningitis presenting with a minimal Glasgow Coma Scale score



(A) Generalized cerebral edema with signs of pseudo-subarachnoid hemorrhage; (B) subdural empyema; (C) generalized cerebral edema indicating severe cerebral inflammation; (D) hydrocephalus.

the Glasgow Outcome Scale and 2 as severely disabled requiring nursing home admission. All 11 patients presenting with either bilaterally absent pupillary light responses or bilaterally absent corneal reflexes died (table 3). Furthermore, all 9 patients with signs of septic shock on admission died; septic shock was defined as diastolic blood pressure <60 mm Hg, systolic blood pressure \leq 90 mm Hg, or heart rate \geq 120 beats per minute. The mortality rate and frequency of sequelae were similar when considering only patients who did not receive sedative medication on admission (table e-2).

The causes of death in the 18 deceased patients were as follows: extensive neurologic damage due to meningitis (6 patients), acute brain herniation shown on cranial imaging (4 patients), withdrawal of care because of poor neurologic prognosis (2 patients; care was withdrawn 2 and 3 days after admission), multiorgan failure or septic shock (2 patients each), and cardiac arrest or delayed cerebral thrombosis (1 patient each).¹⁵ Autopsy was performed in 3 patients showing severe brain damage in all patients. In 1 patient venous sinus thrombosis was identified that was not diagnosed prior to autopsy.

Table 2 Complications and outcome of 30 patients with bacterial meningitis presenting with a minimal coma score

Characteristic	n/N (%) or median (range)
Systemic complications	
Respiratory failure	15/25 (60)
Pneumonia	6/26 (23)
Hyponatremia	4/27 (15)
Neurologic complications	
Cerebral infarction	3/30 (10)
Subdural empyema	2/30 (7)
Hearing impairment	4/30 (13)
Seizures	7/30 (23)
Outcome	
GOS 1	18/30 (60)
GOS 2	0
GOS 3	2/30 (7)
GOS 4	3/30 (10)
GOS 5	7/30 (23)
Time to death, d ^a	2 (1-22)
Causes of death	
Extensive neurologic damage due to meningitis	6/18 (33)
Withdrawal of treatment	2/18 (11)
Brain herniation on CT	4/18 (22)
Multiorgan failure	2/18 (11)
Septic shock	2/18 (11)
Cardiac arrest	1/18 (6)
Delayed cerebral thrombosis	1/18 (6)
Neurologic sequelae	
Cognitive impairment	4
Poor general condition	2
Bilateral hearing loss	1
Hemiparesis	1

Abbreviation: GOS = Glasgow Outcome Scale.
^aData concerning 18 deceased patients.

DISCUSSION Our study shows that a small minority of patients with community-acquired bacterial meningitis presents with a minimal score on the Glasgow Coma Scale (3%). Although the majority of these patients had an unfavorable outcome (77%) and many patients died (60%), the number of patients who recovered completely was substantial. We could not identify clinical parameters predictive for favorable outcome, for example epileptic seizures or sedative drugs. However, patients presenting with a minimal Glasgow Coma Scale score on admission and bilaterally absent pupillary light responses, bilaterally absent corneal reflexes, or signs of septic

Table 3 Clinical characteristics of patients with bacterial meningitis presenting with a minimal coma score with good outcome and with poor outcome

Characteristic	Favorable outcome ^a (n = 10)	Unfavorable outcome ^b (n = 20)
Symptoms and signs on admission		
Seizures	3/10 (30)	7/20 (35)
Sedation	2/10 (20)	3/20 (15)
Septic shock	0/6	9/20 (45)
Abnormal cranial CT	5/9 (56)	13/18 (72)
Generalized edema	2/9 (22)	6/18 (33)
Hydrocephalus	1/9 (11)	4/18 (22)
Indexes of inflammation in the CSF ^c		
Leukocytes <1,000 cells/mm ³	1/10 (10)	9/17 (53)
Protein, median (IQR)	5.5 (2.7–7.1)	5.4 (3.9–8.2)
CSF culture		
<i>Streptococcus pneumoniae</i>	9/10 (90)	17/20 (85)
Adjunctive dexamethasone	10/10 (100)	15/19 (79)

Abbreviations: GOS = Glasgow Outcome Scale; IQR = interquartile range.

Data are n/N (%), unless otherwise specified.

^aFavorable outcome is defined as GOS 4–5.

^bUnfavorable outcome is defined as GOS 1–3.

^cCSF leukocyte count was determined in 27 patients and CSF protein level in 28 patients.

shock on admission all died. Physicians confronted with a patient with bacterial meningitis presenting with a minimal Glasgow Coma Scale score should be aware that at least 1 out of 5 patients will make a full recovery.

Neuroimaging showed that 1 out of 4 patients with bacterial meningitis presenting with a minimal score on the Glasgow Coma Scale have cerebral abnormalities such as hydrocephalus or subdural empyema, which may require emergency neurosurgery. Hydrocephalus and empyema rarely complicate bacterial meningitis (3%–5% of patients) but have been associated with high rates of death and unfavorable outcome.^{16–18} Early identification and subsequent neurosurgical treatment of these complications may improve prognosis. Therefore, immediate cranial imaging should be a priority in patients with a minimal score on the Glasgow Coma Scale on admission to rule out treatable conditions. Because of the risk of increasing brain shift due to lumbar puncture, cranial imaging should precede lumbar puncture in all patients with a minimal Glasgow Coma Scale score to rule out space-occupying lesions causing brain shift.⁸ Antibiotic therapy and adjunctive dexamethasone therapy if indicated should be started before sending the patient to the imaging room. Although some authors have advocated the use of continuous ICP measuring and ICP lowering by use of CSF drainage and medication, the benefit of ICP management in these patients is still unclear.^{19,20}

The abnormal conscious state could be explained by potentially reversible causes, such as seizures, sedative medication, or muscle relaxants, in a subgroup

of patients (47%). However, these patients had similar outcomes compared to the other patients, suggesting that seizures and the need for intubation are markers of disease severity rather than indicators of a reversible cause of an abnormal conscious state. A minimal score on the Glasgow Coma Scale was preceded by epileptic seizures in 33% of patients and 5 patients received antiepileptic or sedative medication as treatment for seizures. Epilepsy has previously been described in 17% of patients with bacterial meningitis.²¹ If no clear explanation for a minimal coma score other than severe inflammation can be found, an EEG should be performed. This is also true for those patients with a waxing and waning level of consciousness. In 9 patients, signs of septic shock were present on admission and likely contributed to the minimal Glasgow Coma Scale score. Three of them also had seizures and one received sedative medication; in the other 5 patients, there was no explanation for the minimal coma score other than septic shock. Stabilization of hemodynamics is of the utmost importance early during sepsis and should have priority in patients with meningitis with concomitant sepsis. Despite aggressive management of the patients with sepsis included in our study, all patients with signs of septic shock on admission eventually died.

This study has several limitations. First, several clinical characteristics of patients with a minimal Glasgow Coma Scale score on admission were not routinely captured in the case record form (for example, brainstem reflexes, anisocoria, sedative medication), but these data were collected retrospectively. Furthermore, patients with a minimal score on the Glasgow Coma Scale may have been missed: patients with bacterial meningitis presenting with a minimal coma score may have severe brain edema, prohibiting a lumbar puncture. Another reason to withhold a lumbar puncture may be diffuse intravascular coagulation, which may occur due to concomitant sepsis. In patients with meningitis with predominant signs of septic shock, meningitis may be missed because the typical sign of meningitis, neck stiffness, is often absent in comatose patients. All these factors may have led to an underestimation of the incidence of a minimal Glasgow Coma Scale score in patients with bacterial meningitis. Furthermore, this is an observational study, and all treatment decisions (for instance to place CSF catheters, operate for subdural empyema, or use ICP management) were at the discretion of the treating physician. Therefore, treatments between patients were different, which is likely to have influenced outcome. This implies our study cannot be used to determine treatment effects, but it does reflect clinical practice as it currently is in the Netherlands. Finally, only patients with positive CSF cultures were included. Negative CSF cultures are estimated to occur in 11%–20% of patients with bacterial meningitis.^{22–24} However, the clinical

presentation of patients with culture-positive bacterial meningitis and patients with culture-negative bacterial meningitis was reported to be similar.

Patients with community-acquired bacterial meningitis rarely present with a minimal score on the Glasgow Coma Scale, but this condition is associated with high rates of morbidity and mortality. However, 1 out of 5 of these severely ill patients will make a full recovery, stressing the continued need for aggressive supportive care.

AUTHOR CONTRIBUTIONS

Marjolein Lucas performed the data analysis and wrote the manuscript. Matthijs Brouwer performed the data analysis and wrote the manuscript. Arie van der Ende wrote the manuscript. Diederik van de Beek performed the data analysis, wrote the manuscript, is the principal investigator of the study, and provided funding.

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DISCLOSURE

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