Community-acquired Bacterial Meningitis in Adults With Cerebrospinal Fluid Leakage

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Background. Cerebrospinal fluid (CSF) leakage is a risk factor for developing bacterial meningitis.

Methods. We analyzed episodes of community-acquired bacterial meningitis associated with CSF leakage from a prospective nationwide cohort study.

Results. CSF leakage was identified in 65 episodes of 2022 episodes (3%) in 53 patients. The cause of CSF leakage was identified in 49 of 65 episodes (75%), which most commonly consisted of ear-nose-throat surgery (19 of 49 episodes [29%]) and remote head trauma (15 of 49 episodes [23%]). The episode was a recurrent meningitis episode in 38 patients (59%). Of the recurrent episodes, 27 had known CSF leakage (71%) of whom 20 (53%) had previous surgery aiming to close the leak. Nine patients (38%) with known CSF leakage had been vaccinated (23-valent pneumococcal vaccine in 9 patients, meningococcal serogroup C vaccine in 2, meningococcal serogroup A and Haemophilus influenzae type b vaccine each in 1 patient). Streptococcus pneumoniae was cultured in 33 episodes (51%) and H. influenzae in 11 episodes (17%). The most common pneumococcal serotypes were 3 (4 episodes), 35B, 9N, 38, and 15C (each 2 episodes). Haemophilus influenzae was unencapsulated in all 10 episodes with known capsule type. The outcome was unfavorable in 8 episodes (12%) and no patient died.

Conclusions. Bacterial meningitis in patients with CSF leakage has a high recurrence rate, despite surgical repair or vaccination, and outcome is generally favorable. CSF leakage should be suspected in patients with bacterial meningitis presenting with liquorrhea, recurrent meningitis, or with disease caused by H. influenzae.

Keywords. cerebrospinal fluid leakage; risk factor; bacterial meningitis.

Risk factors for community-acquired bacterial meningitis include immunocompromise, distant foci of infection, and anatomic deficits in the natural barriers of the brain [1–4]. Anatomic defects can be caused by congenital abnormalities of the skull, through contiguous spread of infection during ear and sinus infections, or after neurosurgery, ear-nose-throat (ENT) surgery, or neurotrauma, which can all lead to cerebrospinal fluid (CSF) leakage [5, 6]. Bacterial meningitis in patients with CSF leakage can be classified as community acquired, in case of anatomic defects or contiguous spread of infection, or nosocomial or healthcare-associated meningitis after surgery for trauma [5, 7, 8]. Symptoms suggestive of CSF leakage include rhinorrhea and otorrhea, but CSF leakage may also go unnoticed [9]. In patients with skull-base fracture due to head trauma, CSF leakage resolves spontaneously within 24 hours after onset [10, 11], but once persistent, meningitis occurs in 7–30% of patients [4, 11, 12]. Cerebrospinal fluid leakage has previously been reported in 3–8% of patients with community-acquired bacterial meningitis and in 38% of patients with recurrent meningitis [13–16]. We evaluated patients with bacterial meningitis associated with identified CSF leakage from a prospective nationwide cohort study in adults with community-acquired bacterial meningitis.

METHODS

In the MeninGene study, a nationwide observational cohort study in the Netherlands, we prospectively included 2022 episodes of community-acquired bacterial meningitis. Methods of the cohort have been described in detail previously [13]. In summary, patients over 16 years old with CSF culture-confirmed community-acquired bacterial meningitis were included between January 2006 and December 2017. The patients were listed in the database of the Netherlands Reference Laboratory for Bacterial Meningitis; this database receives CSF and blood samples from over 85% of all patients with bacterial meningitis in the Netherlands and provides daily updates to the researchers after which the treating physicians were contacted.
Written informed consent was obtained from all participating patients or their legal representatives. We excluded patients with hospital-acquired meningitis, patients with recent (within 1 month) head injury or neurosurgery, and patients with neurosurgical devices.

Data on patients’ characteristics, symptoms and signs on admission, laboratory results, radiological examination, treatment, and outcome were prospectively collected with an online case record form (CRF). In this CRF we defined predisposing factors for developing bacterial meningitis such as otitis media, sinusitis, pneumonia, endocarditis, remote neurosurgical procedure or head trauma, and an immunocompromised state (eg, caused by use of immunosuppressive drugs, splenectomy, diabetes mellitus, cancer, alcoholism, or human immunodeficiency virus). The CRF also included a standard question on the presence or absence of CSF leakage, of which the judgment was left to the discretion of the treating physician. If CSF leakage was reported, additional information was retrospectively collected to the discretion of the treating physician. If CSF leakage was reported, additional information was retrospectively collected and all discharge letters were screened for causes of leakage, duration of leakage, the presence of liquorrhea, number of recurrent episodes, vaccination policy, and treatment of CSF leakage. At discharge, neurological examination was performed and this outcome was graded according to the Glasgow Outcome Scale (GOS), with outcome scores varying from 1 (death) to 5 (good recovery). A favorable outcome was scored as 5 and an unfavourable outcome was scored as 1–4.

Statistical analyses were conducted with the use of SPSS statistical software, version 24 (SPSS, Inc). We used descriptive statistics for baseline characteristics. To identify differences between episodes in patients with and without CSF leak–associated bacterial meningitis we used Mann-Whitney U test for continuous data. For categorical data the chi-square test and Fisher’s exact test were used. All tests were 2-tailed, and \( P < .05 \) was considered significant.

RESULTS

Over the 12-year period, CSF leakage was reported in 65 of 2022 episodes (3%) of community-acquired bacterial meningitis (Table 1) in 53 patients. The median age was 51 years (interquartile range [IQR], 40–61 years) and 33 were male (62%). Upon admission, CSF leakage was reported in 40 of 65 episodes (62%), most commonly rhinoliquorrhea (31 of 40 episodes [76%]). On presentation, the triad of fever, neck stiffness, and altered mental status was present in 20 of 63 episodes (32%); and in 43 of 64 episodes (67%) the duration of symptoms was shorter than 24 hours. In 31 of 65 episodes (48%), the patients presented with a Glasgow Coma Scale (GCS) score of less than 14, indicating an altered mental state. The duration of symptoms at the moment of presentation was shorter in episodes with CSF leak–associated meningitis compared with other meningitis episodes included in the cohort (<24 hours in 43 of 64 [67%] vs 869 of 1877 [46%]; \( P = .001 \)) (Supplementary Table 1). Fewer patients presented with an altered mental state, defined as a score on the GCS of less than 14, in episodes associated with a CSF leak (31 of 65 [48%] vs 1364 of 1945 [70%]; \( P < .001 \)). The cause of CSF leakage was identified in 49 episodes (75%): ENT surgery in 19 episodes (38%), remote head trauma in 15 (31%), previous neurosurgery in 4 (8%), malignancy in 2 (4%), a congenital defect in 6 (12%), and 3 (6%) were diagnosed with idiopathic intracranial hypertension (Table 1).

Thirty-eight of 65 episodes (59%) had a history of meningitis prior to the current episode. In 20 of 38 episodes (53%), the recurrence occurred despite previous surgery aimed at closing the leak. Of the patients with a first episode of CSF leak–associated meningitis, 10 of 27 episodes (37%) were due to a previously identified CSF leak. Other predisposing factors for bacterial meningitis than CSF leakage were present in 23 of 65 episodes (35%), most commonly ear or sinus infections (16 of 23 [70%]) and pneumonia (4 of 23 [17%]). An immunocompromised state was present in 7 of 65 episodes (11%), which was due to the use of immunosuppressive drugs (n = 2), diabetes (n = 3), or alcoholism (n = 2).

Brain imaging was performed in 53 of 65 episodes (82%) (Figure 1) and consisted of cranial computed tomography (CT) in all 53 episodes and cranial magnetic resonance imaging (MRI) with 3-dimensional (3D) constructive interference in steady state (CISS) in 11 of 53 episodes (21%). Cerebrospinal fluid markers (β-2 transferrin test and β-trace) were used in 17 episodes and confirmed CSF leakage in 14 episodes. Cranial imaging could localize the anatomic location of CSF leakage in 60 of 65 episodes (92%). In 4 additional episodes (6%) the CSF leakage was revealed by a β-2 transferrin test, and in 1 episode (2%) the CSF leak was found using myelography with intra-thecal contrast. For 27 of 65 episodes (42%), endoscopic surgical repair of the defect was scheduled after recovery. Surgical outcome in these episodes could be retrieved in 17 episodes (63%). For 11 of 17 episodes it was the first attempt of surgical repair and had a success rate of 91% (10 of 11 episodes) after a follow-up between 3 months and 6 years.

Lumbar puncture was performed in all episodes and showed a median opening pressure of 42 cm H2O (IQR, 32–51 cm H2O). The median CSF leukocyte count in episodes with CSF leak–associated meningitis was 4870 (IQR, 1840–7927), and an elevated white blood cell count (WBC) in CSF of over 1000 cells/mm³ was present in 54 of 61 episodes (89%). In 57 of 65 episodes (88%) at least 1 independent predictor of bacterial meningitis (glucose concentration, <1.9 mmol/L; ratio of CSF glucose concentration to blood glucose concentration, <0.23; protein concentration, >2.20 g/L; WBC count, >2000 cells/mL; or CSF neutrophil count, >1180 cells/mL) was present in the CSF [17].

The CSF culture in episodes with CSF leak–associated meningitis identified the causative organism in 53 of 65 episodes
In 65 episodes of bacterial meningitis, Streptococcus pneumoniae was identified in 33 (51%) episodes and Haemophilus influenzae in 11 (17%) episodes. Other causative agents included Streptococcus agalactiae in 4 episodes (6%), Streptococcus salivarius in 3 episodes (5%), Streptococcus mitis in 3 episodes (4%), Neisseria meningitidis in 1 episode (2%) and Streptococcus agalactiae in 1 episode (2%).

### Table 1. Characteristics of 53 Patients With a Cerebrospinal Fluid Leakage With 65 Bacterial Meningitis Episodes

| Characteristics | Values | Characteristics | Values |
|-----------------|--------|-----------------|--------|
| Median (IQR) age, y | 49 (35–61) | Index of CSF inflammation | 4870 (1840–7927) |
| Male sex | 40/65 (62) | Leukocyte count (cells/mm³) | <100 cells/mm³ |
| Cause of CSF leak | | | 1/65 (2) |
| Remote head trauma | 15/65 (23) | <1000 cells/mm³ | 7/65 (12) |
| Neurosurgery | 4/65 (6) | Median (IQR) protein, g/L | 2.9 (1.7–5.4) |
| ENT surgery | 19/65 (29) | Median (IQR) CSF to blood glucose ratio | 0.2 (0.02–0.37) |
| Congenital | 6/65 (9) | Median (IQR) blood chemical test result | |
| Tumor | 2/65 (3) | C-reactive protein, mg/L | 29.9 (8–78) |
| Other | 3/65 (5) | Thrombocytes, ×10¹²/L | 225 (191–266) |
| Unknown | 16/65 (25) | Causative organism | |
| Presumed onset time of CSF leak | | | |
| ≤1 year | 2/37 (5) | Streptococcus pneumoniae | 33/65 (51) |
| >1 year | 16/37 (43) | Haemophilus influenzae | 11/65 (17) |
| ≥10 years | 19/37 (51) | Neisseria meningitidis | 1/65 (2) |
| Unrevealed leak at first episode | 17/65 (26) | Other organism | 11/65 (17) |
| CSF leak identified on CT/MRI | 60/65 (92) | Negative culture | 9/65 (14) |
| Liquorrhea | 40/65 (62) | Transfer to ICU department | 20/64 (31) |
| Rhinoliquorrhea | 3/40 (76) | Impaired consciousness during admission | 19/62 (31) |
| Otoliquorrhea | 8/40 (20) | Systemic complications | 11/64 (17) |
| Both | 1/40 (3) | Respiratory failure | 5/63 (8) |
| Previous vaccination | 9/24 (38) | Circulatory shock | 0/62 (0) |
| Previous surgery for CSF leakage | 23/65 (35) | Neurologic complications | 25/60 (42) |
| Surgery during or after admission | 27/65 (42) | Seizures | 10/64 (16) |
| Recurrence | 38/65 (59) | Cerebrovascular accident | 0/64 (0) |
| 1 time | 15/65 (23) | Score on GOS | 1/65 (0) |
| >2 times | 15/65 (23) | 1 (Death) | 0/65 (0) |
| >5 times | 8/65 (12) | 2 (Vegetative state) | 0/65 (0) |
| Predisposing factors | 23/65 (35) | 3 (Severely disabled) | 1/65 (2) |
| Immunocompromised state | 7/65 (11) | 4 (Moderately disabled) | 7/65 (10) |
| Pneumonia | 4/65 (6) | 5 (No or minor disability) | 57/65 (88) |
| Otitis media | 8/65 (12) | Sequelae at discharge | 12/65 (19) |
| Sinusitis | 9/65 (14) | Cognitive impairment | 4/66 (9) |
| Symptoms on presentation | Mono- or hemiparesis | 0/68 (0) |
| Headache | 55/60 (92) | Cranial nerve palsy | 6/47 (13) |
| Nausea | 40/58 (69) | | |
| Neck stiffness | 48/62 (74) | | |
| Temperature ≥38°C | 47/64 (73) | | |
| Focal neurological deficits | 13/65 (20) | | |
| Triad of symptoms | 20/63 (32) | | |
| Score on GCS | | | |
| Median (IQR) | 14 (11–15) | | |
| <14 | 31/65 (48) | | |
| ≤8 | 6/65 (9) | | |

Data are presented as n/N (%) unless otherwise noted.

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; ENT, ear-nose-throat; ESR, erythrocyte sedimentation rate; GCS, Glasgow Coma Scale; GOS, Glasgow outcome scale; ICU, intensive care unit; IQR, interquartile range; MRI, magnetic resonance imaging.

*Other etiology: idiopathic intracranial hypertension, enlarged Mrikei’s cave.

*Focal neurological deficits defined as aphasia or hemiparesis or cranial nerve palsies and hearing loss.

*Triad of symptoms = fever, neck stiffness, and change in mental status.

*GCS ≥14 indicates a change in mental status, ≤10 indicates coma.

*Other organisms: Streptococcus salivarius, Streptococcus agalactiae, Escherichia coli, Streptococcus mitis.

*Neurological complications defined as impaired consciousness or seizures or focal neurological deficits or cerebrovascular accidents or sinus thrombosis.
meningitidis in 1 episode (2%) and Escherichia coli in 1 episode (2%). The causative pathogen was not identified in 9 of 65 episodes (14%). The distribution of serotypes of S. pneumoniae was type 3 in 4 episodes (9%); types 35B, 9N, 38, or 15C in 2 episodes each (6%); and types 4, 8, 31, 34, 22F, 35F, 16F, 23A, 11A, 6A, 15B, 33E, 19F, 10A, 6C, 15A, or 24F in 1 episode each (3%). The serotypes of H. influenzae were unencapsulated in all 10 episodes in which capsule type was assessed. The serotype of N. meningitides was type B. Antibiotic treatment consisted of amoxicillin and ceftriaxone according to protocol in 27 patients (42%), whereas 16 patients (25%) received monotherapy third-generation cephalosporins, 10 patients (15%) received penicillin or amoxicillin monotherapy, and 12 (18%) received a different regimen. Differences in initial antibiotic treatment were not associated with outcome.

Among the patients with known CSF leakage, vaccination status could be retrieved in 24 of 65 episodes (40%). Of these, 9 patients (38%) were vaccinated (23-valent pneumococcal polysaccharide vaccine [PPV-23] in 9 patients, 1 patient with H. influenzae type b [Hib] conjugate vaccine, meningococcal serogroup C conjugate vaccine in 2 patients, and meningococcal serogroup A conjugate vaccine in 1 patient) (Table 2). Among 9 episodes in 9 vaccinated patients, 2 (22%) were documented as vaccination failures in 2 patients. Both were infected by serotype 7F pneumococci despite vaccination with PPV-23.

Neurological complications in episodes with CSF leak-associated meningitis occurred in 25 of 60 episodes (42%) and systemic complications in 11 of 64 episodes (17%). In 8 of 65 episodes (12%) an unfavorable outcome occurred and no patients died. The outcome did not significantly differ between patients with a first episode or a recurrence (Supplementary Table 2). The rate of favorable outcome (GOS 5) was higher in patients with CSF leak-associated meningitis compared with other episodes (57 of 65 [88%] vs 1231 of 1957 [63%]; P < .001) (Supplementary Table 1).

DISCUSSION

Our study shows that CSF leakage was identified in a small minority of patients with community-acquired bacterial meningitis (3%). The most common causes of leakage were ENT surgery and remote head trauma, which is consistent with previous studies [11, 12, 14, 18, 19]. The most common causative pathogens are S. pneumoniae and H. influenzae, and the outcome of these episodes is generally favorable.

Prior studies in patients with CSF leak-associated bacterial meningitis are scarce. The relatively favorable outcome has been described previously in patients with recurrent bacterial meningitis episodes [14]. This study hypothesized that due to the awareness of bacterial meningitis, either because of a previous episode or counseling by their physician, patients may recognize bacterial meningitis symptoms early and present themselves to the hospital [14]. Our findings are in line with this hypothesis and showed that patients with CSF leak-associated meningitis

Table 2. Vaccination Status

| Causative Agent | Pathogen Serotype | Vaccine          |
|-----------------|-------------------|-----------------|
| Streptococcus mitis | … | PPV-23 |
| Streptococcus mitis | … | PPV-23 |
| Streptococcus pneumoniae | 7F | PPV-23 + Men-A + Men-C |
| Haemophilus influenzae | Unencapsulated | PPV-23 + Hib + Men-C |
| Streptococcus pneumoniae | 7F | PPV-23 |
| Streptococcus pneumoniae | 24F | PPV-23 |
| Unknown causative agent* | … | PPV-23 |
| Unknown causative agent* | … | PPV-23 |

Abbreviations: Hib, H-influenzae type b conjugate vaccine; Men-A, group A conjugate meningococcal vaccine; Men-C, group C conjugate meningococcal vaccine; PPV-23, 23-valent pneumococcal polysaccharide vaccine.

*No bacteria cultured.
presented more frequently less than 24 hours of symptom onset compared with those without CSF leak.

In our cohort nearly all CSF leaks were identified with cranial imaging. Modern cranial imaging techniques such as CT scan and MRI 3D-CISS can effectively be used to localize the anatomic location of the CSF leakage [20, 21]. Identification of the CSF leak is essential for surgical repair. Our study shows that endoscopic surgical repair is successful in the majority of patients, especially when this is a first attempt (91%). This success rate is in line with previous reviews that reported rates of successful repair ranging from 60% to 100%, with an average of 90% [22–24]. In all patients with recurrent or persisting leakage, consultation with a neurosurgeon or otolaryngologist is warranted to evaluate the necessity of reconstruction of the defect to prevent further episodes [4, 12, 14, 25, 26]. Nevertheless, we identified a subgroup of patients with persistent CSF leakage despite various attempts at surgical repair. Previous retrospective studies suggested that this might be due to various factors that can impact the effectiveness of endoscopic repair, such as duration of the leak, leak etiology, size of the leak, CSF leak location, body mass index, type of identification that was used, and patient’s comorbidity [23, 24]. Surgical repair of defects that have existed for several years is probably more prone to fail when compared with leaks that are identified and repaired shortly after onset. This might be explained by the mucosal lining, instead of simple dural tearing in the acute phase [24]. In these patients, the risk of recurrent meningitis episodes increases with the duration of leakage [4, 11], and therefore early identification and adequate treatment with surgical repair or vaccination.

The episodes of CSF leakage–associated meningitis were predominantly caused by *S. pneumoniae* and *H. influenzae*. Previous studies have suggested to consider a disruption of the S. pneumoniae and therefore early identification and adequate treatment with vaccines in patients presenting with community-acquired bacterial meningitis and CSF leak. The relatively mild disease course resulted in a better outcome in patients with CSF leak–associated bacterial meningitis compared with patients with meningitis not associated with a CSF leak. There are several explanations for this relatively favorable outcome. First, we identified fewer indicators of sepsis in episodes with CSF leakage, such as low CSF leukocyte counts, which have been associated with a high bacterial load, systemic complications and unfavorable outcome [28, 29]. Second, there is a relatively high rate of *H. influenzae* in CSF leak–associated meningitis episodes, and this pathogen has been associated with a less severe clinical course and favorable outcome [30]. Finally, patients with episodes of CSF leak–associated meningitis were significantly younger and had less comorbidity, which also have been identified as predictors of poor outcome [2, 13].

There are several limitations to this study. First, the presence of CSF leakage was initially recorded by the treating physician, which could have led to both over- and underestimation of the rate of CSF leak. However, as all reported cases were confirmed by cranial imaging or a CSF protein marker, overestimation could be ruled out. Underestimation of the frequency of CSF leaks could have occurred because small, occult CSF leaks may have been missed. Furthermore, in patients who presented with acute bacterial meningitis who died within the first days, CSF leaks may have gone unnoticed. Additionally, because all patients who do not survive the first episode cannot develop a second episode, the outcome data are possibly skewed toward a better prognosis resulting in biased results. Therefore, the proportion we found should be considered the minimal frequency. Second, this is a prospective observational study with clinical data collected through an online CRF, which was retrospectively supplemented with additional information from discharge letters, such as cause of leak, duration of leak, previous surgery, vaccination status, and serotypes. For some patients, this specific information was not described in discharge letters and thus registered as unknown, which might have led to a less accurate description of patients’ characteristics. Finally, only culture-proven bacterial meningitis episodes were included in the study while negative CSF cultures occur in 11–30% of episodes with bacterial meningitis, and this may be more common in CSF leak–associated meningitis episodes [7, 14]. Because we performed a nationwide study we were able to describe a representative group of patients with CSF leak–associated community-acquired bacterial meningitis. Furthermore, our prospective approach ensured the collection of comprehensive data on predisposing factors and causes of CSF leakage, clinical characteristics, spectrum of causative pathogens, and outcome.

In conclusion, this study shows that patients with CSF leak–associated bacterial meningitis have a relatively high recurrence rate, despite attempts to repair the leak or vaccination.
The majority of patients have a relatively mild disease course with a generally favorable outcome. Cerebrospinal fluid leakage should be suspected in those patients with bacterial meningitis presenting with liquorhea, recurrent meningitis, or with disease caused by *H. influenzae*. In these patients, cranial imaging and otolaryngology consultation are recommended.

**Supplementary Data**

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

**Notes**

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