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Recurrent Community-Acquired Bacterial Meningitis in Adults

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Background. Recurrent bacterial meningitis has been found to occur in about 5% of meningitis cases.

Methods. We analyzed adults with recurrent episodes in a prospective nationwide cohort study of community-acquired bacterial meningitis.

Results. Of 2264 episodes of community-acquired bacterial meningitis between 2006 and 2018, 143 (6%) were identified as recurrent episodes in 123 patients. The median age was 57 years (interquartile range [IQR], 43–66), and 57 episodes (46%) occurred in men. The median duration between the first and the current episode was 5 years (IQR, 1–15). For 82 of 123 patients (67%), it was the first recurrent episode, 31 patients had 2–5 previous episodes (25%), 2 had 6–10 episodes (2%), and 2 had >10 episodes (2%). Predisposing factors were identified in 87 of 118 patients (74%) and most commonly consisted of ear or sinus infections (43 of 120, 36%) and cerebrospinal fluid leakage (37 of 116, 32%). The most common pathogens were *Streptococcus pneumoniae* (93 of 143, 65%) and *Haemophilus influenzae* (19 of 143, 13%). The outcome was unfavorable (Glasgow outcome scale score, <5) in 24 episodes with recurrent meningitis (17%) vs 810 for nonrecurrent meningitis patients (39%, $P < .001$). Six of 143 died (4%) vs 362 of 2095 patients (17%, $P < .001$).

Conclusions. Recurrent meningitis occurs mainly in patients with ear or sinus infections and cerebrospinal fluid leakage. Predominant causative pathogens are *S. pneumoniae* and *H. influenzae*. The disease course is less severe, resulting in lower case fatality compared with nonrecurrent meningitis patients.

Keywords. recurrent meningitis; bacterial meningitis; predisposing factor; vaccination.

Community-acquired bacterial meningitis is a life-threatening infection of the central nervous system [1]. The mortality rate in high-income countries is approximately 20%, and neurological sequelae occur in almost half of the surviving patients [2]. Recurrent episodes of bacterial meningitis have been described in 5% of community-acquired bacterial meningitis cases and have been associated with a relatively favorable prognosis [3]. Several factors have been identified that predispose to recurrent meningitis, such as cerebrospinal fluid (CSF) leakage, remote head injury, and an immunocompromised state [3]. Previous studies have recommended early identification of these predisposing factors to prevent further recurrences [3–6].

The introduction of routine vaccination of children with protein-polysaccharide conjugate vaccines against most common causative pathogens of bacterial meningitis has reduced the incidence of bacterial meningitis and the prevalence of common causative pathogens of meningitis [7, 8]. The 2016 European Society for Clinical Microbiology and Infectious Diseases guideline on community-acquired bacterial meningitis advises to routinely vaccinate patients after community-acquired pneumococcal meningitis (23-valent pneumococcal polysaccharide vaccine [PPV-23], pneumococcal conjugate vaccine [PCV]) as well as those with meningitis and CSF leakage (PPV-23, PCV, *Haemophilus influenzae* type b (Hib), meningococcal serogroup ACWY, and serogroup B vaccines) [9]. However, whether these vaccines are routinely administered and reduce the incidence of recurrent episodes is unclear.

We evaluated patients with recurrent meningitis episodes from a nationwide prospective cohort study to summarize predisposing factors, pathogen distribution, vaccination status, and outcome.

METHODS

We prospectively included adult patients with community-acquired bacterial meningitis in the MeninGene study, a nationwide cohort study in the Netherlands, from March 2006 to July

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2018. The methods of patient identification and inclusion have been described previously [1]. In short, the patients were listed either in the database of the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM) or reported to the investigators by the treating physician. The NRLBM receives clinical CSF and blood isolates from more than 85% of all patients with bacterial meningitis in the Netherlands and provides daily updates to the researchers. The treating physicians were then contacted by telephone with the request to inform the patients or their legal representatives and obtain written informed consent for participation for this study. We included adult patients (aged ≥16 years) with confirmed community-acquired bacterial meningitis. We defined bacterial meningitis as a bacterial pathogen in the CSF or when the CSF chemistry results were indicative for bacterial meningitis according to the Spanos criteria [10] or a Spanos criterion in combination with a pathogen identified in the blood culture, CSF polymerase chain reaction (PCR), or CSF antigen. Episodes of nosocomial or post-traumatic bacterial meningitis were excluded, for example, meningitis within 1 month after head trauma or neurosurgery, hospital-acquired meningitis defined as meningitis during hospital admission or within 1 week after discharge, and patients with neurosurgical devices [1].

We evaluated patients with 1 or more recurrent episodes of community-acquired bacterial meningitis. Extensive data on patients' characteristics, medical history, symptoms and signs on admission, laboratory results, radiological examination, treatment, and outcome were prospectively collected through an online case record form (CRF). The CRF included a standard question if the current episode is a recurrent episode. When this question was scored as present, unknown, or missing, additional information was retrospectively collected using discharge letters. These detailed discharge letters were screened for number of recurrent episodes, seasonal distribution, vaccination status, use of prophylactic antibiotics, predisposing factors, and causative pathogen including serotype/serogroup. Missing data on vaccination status were retrieved from the general practitioners. Recurrent bacterial meningitis was defined as a second or subsequent episode of bacterial meningitis caused by different organisms or caused by the same pathogen >3 weeks after the completion of therapy for the previous episode. Pathogen distribution of the current and previous episodes was retrieved via the discharge letters and the NRLBM. Pneumococcal isolates were serotyped by agglutination and subtyped using the Quellung method [11]. Meningococcal isolate serogroups were determined using Ouchterlony gel diffusion, which is an immunoprecipitation assay [12].

We defined an immunocompromised state as a primary immunodeficiency, which included hypogammaglobulinemia, late complement component deficiency, common variable immunodeficiency, or as a secondary immunodeficiency, defined as the use of immunosuppressive medication, splenectomy, or due to diseases that influence the immune system (eg, human immunodeficiency virus [HIV] infection) [9].

Neurological examination was performed on admission and at discharge. Level of consciousness was scored using the Glasgow coma scale: a score ≤14 indicates an altered mental state and a score of ≤8 indicates coma. Clinical outcome at discharge was graded according to the Glasgow outcome scale, with outcome scores varying from 1 (death) to 5 (good recovery).

Statistical analyses were conducted using SPSS statistical software, version 24 (SPSS Inc). To identify differences between episodes in patients with a recurrent episode and nonrecurrent episodes, we used the Mann-Whitney *U* test for continuous data. For categorical data, the χ^2 test or Fisher exact test was used. All tests were 2-tailed, and $P < .05$ was considered significant.

RESULTS

Over the 12-year period, 2264 episodes of community-acquired bacterial meningitis were included. Of these, 143 recurrent episodes (6%) were identified among 123 patients. The median age of these patients during the recurrent episodes included in the study period was 57 years (interquartile range [IQR], 43–66), and 57 (46%) were male. The duration between the first episode and the current episode was known for 116 patients (94%), with a median duration of 5 years (IQR, 2–15). For the majority of patients (82 of 117, 70%), the current episode was the first recurrent episode, and 2 patients (2%) had more than 10 recurrent episodes (Table 1). Potential predisposing factors for bacterial meningitis were identified in 87 of 118 patients (74%; missing in 5 patients); ear or sinus infections (43 of 120, 36%), CSF leakage (37 of 116, 32%), and immunocompromised state were the most common (17 of 123, 14%). Most common

Table 1. Characteristics of 128 Recurrent Meningitis Patients

Characteristic	n/N (%) or Median (IQR)
Age, years	57 (43–66)
Male sex	57/123 (46%)
Medical history	
Predisposing factors	87/118 (74%)
CSF leakage	37/116 (32%)
Remote head trauma without sign of CSF leak	4/119 (3%)
Immunocompromised state	17/123 (14%)
Extra meningeal foci of infection	44/123 (36%)
Otitis media or sinusitis	43/120 (36%)
Pneumonia	1/122 (1%)
Number of recurrences	
1	82/117 (70%)
2–5	31/117 (27%)
6–10	2/117 (2%)
>10	2/117 (2%)
Time between first current episode, median (IQR), years	5 (2–15)
Previous vaccination	27/92 (29%)

Abbreviations: CSF, cerebrospinal fluid; IQR, interquartile range.

causes of CSF leakage were ear–nose–throat surgery (10 of 37, 27%) and remote head trauma (9 of 37, 24%). Of the patients with CSF leakage, 15 of 37 (41%) had a recurrent episode despite previous surgical repair. Four of 119 patients (3%) had a history of head trauma without signs of CSF leakage. Predisposing immunocompromising conditions were identified in 17 patients (14%) and included the use of immunosuppressive drugs in 9 (64%), splenectomy in 4 (29%), living with HIV in 2 (14%), and primary immunodeficiencies in 4 patients (29%; complement factor C6 deficiency and mannan-binding lectin deficiency [n = 1], a C7 deficiency [n = 1], an immunoglobulin [Ig] G-2 deficiency [n = 1], and a late-onset hypogammaglobulinemia [n = 1]). Some patients had more than 1 immunocompromised condition.

Recurrent episodes of bacterial meningitis presented with headache in 121 of 131 episodes (92%), neck stiffness in 94 of 131 (72%), fever in 101 of 137 (74%), and an altered mental status in 65 of 143 (46%; Table 2). Compared with nonrecurrent episodes, the duration of symptoms was more often shorter than 24 hours in recurrent episodes (95 of 142 episodes [67%] vs 912 of 2022 episodes [45%, $P < .001$]), and fewer episodes presented with an altered mental state (65 of 143 [46%] vs 1480 of 2089 [71%, $P < .001$]; Table 2).

Brain imaging was performed on presentation and/or during admission in 113 of 143 episodes (76%) and identified abnormalities in 47 of 113 episodes (42%), mainly sinus and/or mastoid opacification (40 of 47 episodes, 85%). Lumbar puncture was performed in all episodes. CSF showed an elevated leukocyte count of more than 1000 cells/ mm^3 in 104 of 137 episodes (76%), with a median of 3190 cells/mm^3 (IQR, 1033–6313). In 117 of 143 episodes (82%), at least 1 independent CSF predictor of bacterial meningitis, according to Spanos, was present in CSF [10].

The causative pathogen was identified in 135 episodes. CSF culture identified the pathogen in 127 of 143 episodes (89%), in 5 episodes (4%) the pathogen was identified by blood culture, in 2 by PCR (2%), and in 1 by both blood culture and PCR (1%). *Streptococcus pneumoniae* was identified in 93 of 135 episodes (69%), *H. influenzae* in 19 of 135 (14%), *Neisseria meningitidis* in 9 of 135 (7%), and *Listeria monocytogenes* in 1 of 135 (1%). Other causative organisms were *Streptococcus agalactiae* (n = 3), *Streptococcus salivarius* (n = 2), *Streptococcus suis* (n = 2), *Streptococcus mitis* (n = 2), *Streptococcus viridans* (n = 2), *Escherichia coli* (n = 1), and *Streptococcus pyogenes* (n = 1). Pneumococcal serotypes were retrieved in 73 of 93 recurrent pneumococcal episodes (78%; Supplementary Table 1) and were most often caused by serotypes 19A (n = 7), 3 (n = 5), 7F (n = 5), 8 (n = 5), 22F (n = 5), and 19F (n = 5). All 19 serotyped *H. influenzae* strains were unencapsulated, of which 2 were β-lactamase–positive and 17 β-lactamase–negative. Meningococcal serogroups were available in 8 of 9 episodes and showed serogroup B in 5 episodes, Y in 2 episodes, and C in 1 episode. Two of 123 patients with recurrent meningococcal meningitis had a known complement deficiency.

Antibiotic treatment consisted of initial empiric therapy with amoxicillin and ceftriaxone according to protocol in 56 of 143 episodes (39%). This initial empiric therapy was adjusted after a pathogen was identified and antibiotic susceptibilities were available to third-generation cephalosporins in 15 of 56 episodes (27%), to penicillin or amoxicillin monotherapy in 33 episodes (59%), to a different regimen in 5 episodes (9%), and was unknown in 1 episode. Whereas in 28 of 143 episodes (36%) monotherapy third-generation cephalosporins were given, 16 (11%) were given penicillin or amoxicillin monotherapy and 19 (13%) were given a different regimen. In 24 episodes, the patients received initial empiric monotherapy third-generation cephalosporins, which was adjusted to penicillin monotherapy. Adjunctive dexamethasone treatment was given in 129 of 142 episodes (91%). Data on prophylactic antibiotics were available for 92 episodes (64%), of which 2 (2%) had a recurrence despite the use of prophylactic antibiotic.

During admission, systemic complications occurred in 43 of 136 episodes (32%). Neurological complications occurred in 48 of 134 episodes (36%; Table 2). The clinical outcome was unfavorable in 24 of 143 episodes (17%), and in 6 of 143 episodes the patient died (4%). The rate of unfavorable outcome was significantly lower compared with nonrecurrent meningitis episodes (810 of 2095, 39%; $P < .001$). The 4% mortality rate in patients with recurrent meningitis was also significantly lower compared with nonrecurrent cases (362 of 2095, 17%; $P < .001$). Five patients with recurrent meningitis died after pneumococcal meningitis and 1 after listeria meningitis.

Available vaccines (PPV-23, PCV-13, PCV-7, MenACWY, MenB) could have covered the bacterial strain of 56 of 143 episodes (39%). Vaccination status could be retrieved in 92 of 143 episodes (64%). Of these, 27 were vaccinated (29%): 20 received PPV23, 5 received PCV13, 5 received meningococcal ACWY vaccine, 8 received meningococcal C vaccine, 5 received Hib, 1 received PcV-7, and in 1 episode the type of vaccination was not specified. Vaccination failure occurred in 10 of 26 episodes (39%; Table 3). Eight episodes occurred due to *S. pneumoniae* 7F (n = 2), 19A (n = 2), and 6B, 10A, 19F, and 23F (n = 1) despite adequate PPV-23 vaccination including these serotypes. One meningococcal C and 1 meningococcal Y episode occurred despite meningococcal ACWY vaccination.

After discharge for the current episode, 34 of 143 (24%) received vaccination that consisted of PPV23 in 23 patients, Hib in 12 patients, meningococcal C vaccine in 11, meningococcal ACWY in 2, meningococcal B in 1, and PCV13 and PCV7 both in 2 patients. There was no difference in the proportion of patients with recurrent meningitis prior to or after the guidelines recommended routine vaccination after pneumococcal meningitis (122 of 1858, 7% vs 21 of 406, 5%; $P = .37$).

Table 2. Recurrent Episodes Compared With Nonrecurrent Episodes

Characteristic	Recurrent Episodes, No. (%)	Nonrecurrent Episodes, No. (%)	*P* Value
Age, median (IQR), years	56 (41–66)	61 (48–70)	<.001
Male sex	67/143 (47%)	1093/2121 (52%)	.30
Medical history			
Previous neurologic deficits	33/139 (24%)	200/2081 (10%)	<.001
Predisposing factors	103/137 (75%)	1113/2028 (55%)	<.001
CSF leakage	46/135 (34%)	34/2082 (2%)	<0.001
Remote head trauma without CSF leak	4/138 (3%)	52/1985 (3%)	.78
Immunocompromised state	19/143 (13%)	219/2121 (10%)	.26
Extra meningeal foci of infection	51/143 (36%)	907/2087 (44%)	.08
Otitis media or sinusitis	49/140 (35%)	717/2018 (36%)	.93
Pneumonia	2/142 (1%)	197/2012 (10%)	<.001
Symptoms at presentation			
Symptoms duration <24 hours	95/142 (67%)	912/2022 (45%)	<.001
Headache	121/131 (92%)	1454/1805 (81%)	<.001
Neck stiffness	94/131 (72%)	1418/1941 (73%)	.76
Temperature ≥38°C	101/137 (74%)	1495/2049 (73%)	.92
Focal neurological deficits [a]	27/143 (19%)	739/2100 (35%)	<.001
Triad of symptoms [b]	34/133 (26%)	794/1980 (40%)	.001
Score on Glasgow coma scale [c]			
Median (IQR)	14 (11–15)	11 (9–14)	<.001
≤14	65/143 (46%)	1480/2089 (71%)	<.001
≤8	19/143 (13%)	426/2089 (20%)	.04
Index of CSF inflammation			
Leukocyte count, median (IQR), cells/mm^3	3190 (1033–6313)	2283 (557–6670)	.14
Protein concentration, g/L	3 (1.7–4.9)	3.8 (2.2–6.1)	.001
CSF to blood glucose ratio (IQR)	0.22 (0.04–0.37)	0.06 (0.012–0.28)	<.001
CSF pressure	35 (29–48)	40 (29–50)	.15
Blood chemical test result			
Erythrocyte sedimentation rate, median (IQR), mm/h	14 (6–47)	42 (23–70)	<.001
C-reactive protein, mg/L	50 (11–134)	195 (92–305)	<.001
C-reactive protein elevated (>10mg/L)	107/143 (75%)	1964/2030 (97%)	<.001
Leukocyte count, $\times 10^9$/L	16 (12–21)	16 (12–22)	.31
Thrombocytes, $\times 10^{12}$/L	224 (186–269)	197 (147–255)	<.001
Causative organism			
Identified by blood culture	85/122 (70%)	1341/1819 (74%)	.33
Identified by CSF culture	127/143 (88%)	1888/2121 (89%)	.94
Streptococcus pneumoniae	93/143 (65%)	1410/2121 (67%)	.72
Haemophilus influenzae	19/143 (13%)	65/2121 (3%)	<.001
Neisseria meningitidis	9/143 (6%)	227/2121 (11%)	.12
Listeria monocytogenes	1/143 (1%)	125/2121 (6%)	.004
Other organism	13/143 (9%)	198/2121 (9%)	1.00
Negative culture	8/143 (6%)	96/2121 (5%)	.53
Complications during admission			
Systemic complications	43/136 (32%)	1023/1963 (52%)	<.001
Respiratory failure	18/137 (13%)	519/2024 (26%)	.001
Circulatory shock	6/137 (4%)	210/1976 (11%)	.02
Pneumonia	8/135 (6%)	317/1953 (16%)	.001
Neurologic complications [d]	48/134 (36%)	1009/1848 (55%)	<.001
Focal neurological deficits	36/138 (26%)	774/1928 (40%)	.001
Cerebrovascular accident	8/140 (6%)	220/1945 (11%)	.05
Seizures	17/140 (12%)	280/1996 (14%)	.61
Hearing loss	21/126 (17%)	463/1684 (28%)	.009
Neurological deficits at discharge			
Focal neurological deficits[a]	15/108 (14%)	308/1354 (23%)	.040
Aphasia	3/111 (3%)	47/1406 (3%)	1.00
Cranial nerve palsy	9/111 (8%)	203/1380 (15%)	.07
Paresis	4/107 (4%)	114/1386 (8%)	.13
Cognitive impairment	14/111 (13%)	279/1380 (20%)	.062

Table 2. Continued

Characteristic	Recurrent Episodes, No. (%)	Nonrecurrent Episodes, No. (%)	*P* Value
Score on Glasgow outcome scale [e]			
1	6/143 (4%)	362/2095 (17%)	<.001
2	0/143 (0%)	6/2095 (0.3%)	1.00
3	3/143 (2%)	101/2095 (5%)	0.15
4	15/143 (11%)	341/2095 (16%)	0.08
5	119/143 (83%)	1285/2095 (61%)	<.001

Abbreviation: CSF, cerebrospinal fluid; IQR, interquartile range; N=143 for recurrent episodes of bacterial meningitis; N=2121 for nonrecurrent bacterial meningitis episodes.

[a] Focal neurological deficits defined as aphasia or hemiparesis or cranial nerve palsies, including hearing loss.

[b] Triad of symptoms = fever, neck stiffness, and change in mental status.

[c] Glasgow coma scale: <14 indicates a change in mental status and ≤8 indicates coma.

[d] Neurological complications during admission defined as seizures or focal neurological deficits or cerebrovascular accidents or sinus thrombosis.

[e] Glasgow outcome scale: 1 indicates death, 2 indicates a vegetative state, 3 indicates severe disability, 4 indicates moderate disability, and 5 indicates mild or no disability.

Using the NRLBM database, pathogen distribution could be retrieved for 327 episodes, including the current episodes and episodes prior to the current cohort study, among 123 patients (Supplementary Figures 1 and 2A–C). CSF cultures were positive in 245 episodes; *S. pneumoniae* in 167 episodes (68%); *H. influenzae* in 29 (12%); *N. meningitidis* in 29 (12%); *S. agalactiae* and *S. salivarius* in 4 (2%); *S. suis* in 3 (1%); *L. monocytogenes*, *S. mitis*, and *S. viridans* in 2 (1%); and *Campylobacter species*, *E. coli*, and *S. pyogenes* all in 1 (0.4%). Twenty-eight of 123 patients (23%) had meningitis episodes caused by 2 different pathogens, 4 patients (3%) had meningitis episodes caused by 3 different pathogens, and 1 patient (1%) had meningitis episodes caused by 4 different pathogens. Six patients had recurrent pneumococcal

Table 3. Vaccination Status and Cause of Recurrent Meningitis

Patient	Type of Vaccination Received	Pathogen	Vaccination Failure
1	PPV-23, Men-C, Hib	*Streptococcus pneumoniae* 6B	Yes
2	PPV-23	*S. pneumoniae* 7F	Yes
3	PPV-23, Men-C, Hib	*S. pneumoniae* 7F	Yes
4	PPV-23, Men-C	*S. pneumoniae* 10A	Yes
5	PPV-23, Men-C	*S. pneumoniae* 19A	Yes
6	PPV-23, Men-C	*S. pneumoniae* 19A	Yes
7	PPV-23, PCV-13, Men-ACWY	*S. pneumoniae*19F	Yes
8	PPV-23, PCV-13, Men-ACWY	*S. pneumoniae* 23B	No
9	PPV-23, Men-C	*S. pneumoniae* 23F	Yes
10	PPV-23	*S. pneumoniae* 24F	No
11	PPV-23	*S. pneumoniae 27*	No
12	PPV-23	*S. pneumoniae* 27	No
13	missing	*S. pneumoniae* [a]	Unknown
14	Men-ACWY	*Neisseria meningitidis C*	Yes
15	Men-ACWY	*N. meningitidis Y*	Yes
16	PCV-13	*Haemophilus influenzae* n.t	No
17	PCV-7. HiB	*H. influenzae* n.t	No
18	PPV-23	*H. influenzae* n.t	No
19	PPV-23	*H. influenzae* n.t	No
20	PPV-23, Men-C, Hib	*H. influenzae* n.t	No
21	PPV-23	*Streptococcus mitis*	No
22	PPV-23	*S. mitis*	No
23	PPV-23	Negative culture	Unknown
24	PPV-23	Negative culture	Unknown
26	PCV-13, Men-C, Hib	Group B streptococcus	No
25	PPV-23	Unknown pathogen [b]	Unknown
27	PPV-23, PCV-13, Men-ACWY	Unknown pathogen [b]	Unknown

Abbreviations: Hib, H-influenzae type b conjugate vaccine; Men-ACWY, group ACWY conjugate meningococcal vaccine; Men-C, group C conjugate meningococcal vaccine; Men-B, group B meningococcal vaccine; PCV-7, 7-valent pneumococcal conjugate vaccine; PCV-13, 13-valent pneumococcal conjugate vaccine; PPV-23, 23-valent pneumococcal polysaccharide vaccine.

[a] No serotype or serogroup was retrieved.

[b] No pathogen was retrieved.

meningitis due to the same serotype, 2 patients had recurrent nontypeable *H. influenzae* meningitis, and 1 patient had recurrent meningococcal meningitis due to the same serogroup (Supplementary Table 2).

DISCUSSION

Our study shows that recurrent meningitis occurs in 6% of episodes and mainly in those with predisposing factors such as CSF leakage, ear or sinus infections, and an immunosuppressive state. Predominant causative pathogens are *S. pneumoniae* and nonencapsulated, nontypeable *H. influenzae*. Disease course was less severe compared with nonrecurrent meningitis patients, leading to a lower case fatality rate.

No underlying risk factor was found in a substantial number of patients with recurrent meningitis (28%). Early identification of the predisposing factor may lead to prevention of new recurrences [4, 13–15]. The active search for predisposing factors should focus on anatomical defects and immunodeficiencies. CSF leaks can be identified with CSF markers (β-2 transferrin test and β-trace) and with cranial imaging techniques such as thin-slice computed tomography of the skull base and magnetic resonance imaging with 3-dimensional constructive interference in steady state. A primary or secondary immunodeficiency can be detected with a careful history and laboratory tests that include quantitative immunoglobulins, specific antibody levels, pre- and post-immunization antibody levels, IgG subclasses, and complement function [16–18]. Recurrent meningococcal meningitis is associated with complement deficiencies, with a recurrence risk of 45% [7, 14, 19]. In our study, 2 patients with a known complement deficiency were included, both with a recurrent meningococcal meningitis. The role of inborn errors of innate immunity in susceptibility of bacterial meningitis and recurrent meningitis, in particular, is unclear. Defects in the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway and chemotaxis have been described to predispose to severe invasive pneumococcal disease, but the frequency and relevance in recurrent bacterial meningitis have not been systematically studied [20–22].

Patients with recurrent bacterial meningitis have a more favorable outcome compared with nonrecurrent meningitis patients. This is in line with previous results of smaller studies [3, 4]. Although speculative, the favorable disease outcome in recurrent meningitis patients can be explained by several factors. First, patients with recurrent meningitis might recognize symptoms of meningitis, promoting early medical attention. Patients with recurrent meningitis presented early with less severe symptoms compared with the nonrecurrent cases. In a disease as deadly as bacterial meningitis, early antibiotic treatment is one of the most important factors for favorable outcome [23]. Second, patients with recurrent meningitis had a lower rate of bacteremia and systemic complications [24, 25]. Episodes are often predisposed by a CSF leakage, which contributes to a better prognosis due to the relatively benign pathophysiology [4]. Third, patients with recurrent meningitis might have a less severe inflammatory response, potentially caused by immunocompromise and inborn errors of innate immunity. Bacterial meningitis is a complex disease with outcomes driven by the host inflammatory response [23]. Patients with less severe inflammatory response might have better disease outcomes. Finally, a competing risk between mortality and recurrence of illness has been described that might explain the favorable outcome, as there is no recurrence of meningitis when a patient has died [3]. The outcome of recurrent meningitis episodes appears to be favorable; however, we have identified a large number of patients with long-term neurological sequelae such as cognitive deficits after bacterial meningitis (32%). This provides further incentive to actively search for underlying conditions to prevent further recurrent episodes [2, 26].

Recurrent meningitis episodes were predominantly caused by *S. pneumoniae* and *H. influenzae*, and we found recurrent meningitis patients to have multiple recurrent episodes due to different pathogens. We found that less than one-third of the patients received vaccination. The benefit of vaccination is uncertain because controlled studies on the effect of vaccination in recurrent meningitis patients are not available, the available vaccines only cover 39% of the bacterial strains that cause recurrent meningitis, and vaccination failures occur [7, 8]. On the other hand, vaccination is minimally invasive, the risk for adverse events is low, and, according to expert opinion, vaccination is indicated in these high-risk patients. Therefore, we do recommend the use of Hib, PPV-23, meningococcal serogroup ACYW, and meningococcal serogroup B after a second bacterial meningitis episode or directly after a first episode in those with a specific risk factor (eg, CSF leak) [4, 27, 28].

There are several limitations to this study. First, this was a prospective observational study with data collected via a CRF and additional data retrospectively collected through discharge letters. For some patients, specific information, such as predisposing factor, number of recurrent episodes, use of prophylactic antibiotics, and vaccination status, was not described in discharge letters and thus registered as unknown, which might have led to a less accurate description of patients' characteristics. Second, some patients were referred to the outpatient clinic for ancillary diagnostics to identify a predisposing factor; unfortunately, no follow-up data could be retrieved. Therefore, underlying conditions predisposing for recurrent meningitis may have been missed. Finally, patients with a positive CSF culture were identified by the NRLBM. This resulted in only a small number of included patients with a negative CSF culture. Negative CSF cultures have been reported to occur in 11%–41% of patients clinically suspected for bacterial meningitis, and this may be more common in recurrent meningitis episodes [3, 28, 29]. Nonetheless, this large nationwide study allowed us to describe a representative group of patients with recurrent community-acquired bacterial meningitis episodes.

In conclusion, recurrent meningitis frequently occurs due to predisposing factors, most commonly ear or sinus infections and CSF leakage. The disease course is more favorable with a lower mortality rate compared with nonrecurrent meningitis patients. Recurrent episodes are predominantly caused by *S. pneumoniae* and *H. influenzae,* and these patients can have multiple recurrent episodes due to different pathogens. We recommend actively searching for a predisposing factor after a second episode of bacterial meningitis and vaccination after a first episode of *S. pneumoniae*, *N. meningitidis*, or *H. influenzae* meningitis; a second episode; or in case of an identified predisposing factor.

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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