

Community-Acquired Recurrent Bacterial Meningitis in Adults

Kirsten S. Adriani,¹ Diederik van de Beek,¹ Matthijs C. Brouwer,¹ Lodewijk Spanjaard,^{2,3} and Jan de Gans¹

Departments of ¹Neurology and ²Medical Microbiology and ³The Netherlands Reference Laboratory for Bacterial Meningitis, Center of Infection and Immunity Amsterdam, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Background. Community-acquired recurrent bacterial meningitis in adults is a relatively rare disease. All previous data were derived from small retrospective case series.

Methods. We prospectively evaluated episodes of recurrent bacterial meningitis in a nationwide cohort study in The Netherlands.

Results. Thirty-four episodes of recurrent bacterial meningitis were identified among 31 patients; 3 patients experienced 2 episodes during the study period. The mean age was 43 years, and 25 (74%) of 34 episodes occurred in men. Predisposing conditions were involved in 26 (77%) of 34 episodes; the most common predisposing conditions were remote head injury (17 [53%] of 32 episodes) and cerebrospinal fluid (CSF) leakage (9 [32%] of 28 episodes). Lumbar puncture revealed an individual CSF indicator of bacterial meningitis for almost all episodes (88%). The outcome was death for 5 (15%) of 34 episodes; 1 additional patient had a suboptimal score on the Glasgow Outcome Scale.

Conclusion. We conclude that most patients with recurrent meningitis are male and have predisposing conditions, which, in most cases, are remote head injury or CSF leakage.

Community-acquired bacterial meningitis is a serious and life-threatening disease. The estimated incidence is 2.6–6 cases per 100,000 adults per year in developed countries, and *Streptococcus pneumoniae* and *Neisseria meningitidis* are the leading causes [1–3]. Recurrent bacterial meningitis has been estimated to occur in 4%–9% of all patients with community-acquired bacterial meningitis; cases have been described after head trauma and neurosurgical procedures, even after several years, and have also been described in patients with congenital malformations or immunocompromised state [2, 4–9]. Most previous data were derived from small retrospective case series [10, 11]. We performed the first prospective nationwide cohort study involving adults with community-acquired bacterial meningitis [12]. In this article, we describe the incidence, clinical features,

complications, and outcome in adults with recurrent community-acquired bacterial meningitis.

METHODS

In the Dutch Meningitis Cohort Study, a nationwide observational cohort study in The Netherlands, 696 episodes of community-acquired acute bacterial meningitis were assessed prospectively. All causative organisms were identified by CSF culture, which yielded *S. pneumoniae* in 352 episodes (51%), *N. meningitidis* in 257 episodes (37%), and other bacteria in 87 episodes (12%). Inclusion and exclusion criteria have been described elsewhere [12]. In summary, eligible patients were aged >16 years, had bacterial meningitis confirmed by culture of CSF, and were listed in the database of The Netherlands Reference Laboratory for Bacterial Meningitis from October 1998 through April 2002. The treating physician was contacted, and informed consent was obtained from participating patients or their legal representatives. The study was approved by our ethics committee. Patients with hospital-acquired meningitis (defined as meningitis that occurred during hospitalization or within 1 week after hospital discharge), neurosurgical devices, and a history of a recent (within <1 month) head trauma or neurosurgical procedure were

Received 26 February 2007; accepted 27 April 2007; electronically published 23 July 2007.

Reprints or correspondence: Dr. Kirsten S. Adriani, Academic Medical Center, University of Amsterdam, Dept. of Neurology H2, P.O. Box 22660, 1100 DD Amsterdam, The Netherlands (k.s.adriani@amc.uva.nl).

Clinical Infectious Diseases 2007;45:e46–51

© 2007 by the Infectious Diseases Society of America. All rights reserved.

1058-4838/2007/4505-00E1\$15.00

DOI: 10.1086/520682

excluded. Recurrent meningitis was defined as a second or subsequent episode of meningitis in a patient that was caused by a different organism than the organism that caused the first episode or by the same organism >3 weeks after the completion of therapy for the first episode. Patients with an altered immune status owing to the use of immunosuppressive drugs or splenectomy, diabetes mellitus, or alcoholism were considered to be immunocompromised. We defined predisposing factors for developing bacterial meningitis, such as otitis, sinusitis, pneumonia, CSF leakage, immunocompromised state, remote neurosurgical procedure, and remote head trauma. Neurosurgical procedures and head trauma were classified as remote when they occurred >1 month before the onset of meningitis. All patients underwent a neurological examination at hospital discharge, and outcome was graded using the Glasgow Outcome Scale. This measurement scale is well validated, with scores varying from 1 (indicating death) to 5 (indicating good recovery). A favorable outcome was defined as a score of 5, and an unfavorable outcome was defined as a score of 1–4. Focal neurological abnormalities were divided into focal cerebral deficits (e.g., aphasia, monoparesis, or hemiparesis) and cranial nerve palsies.

RESULTS

During the 3.5-year period, 34 (4.8%) of 696 episodes of community-acquired bacterial meningitis were classified as recurrent meningitis (table 1). The calculated annual incidence of recurrent bacterial meningitis was 0.12 cases per 100,000 adults. The mean age was 43 years, and 25 episodes (74%) occurred in men. The 34 episodes occurred among 31 patients; the studied episode was the second episode of bacterial meningitis in 25 patients (81%), the third episode in 4 (13%), and the fifth and sixth episodes in 1 patient (3%). Three patients experienced 2 episodes during the study period. The duration between the first episode and the studied episode was known for 22 episodes; the median duration was 4 years (range, 0–29 years). Seven (23%) of 31 patients had neurologic sequelae from a previous episode, which consisted of hearing impairment in 2 patients, cognitive impairment in 2, epilepsy in 1, and an unknown sequelae in 2. Most episodes occurred during winter (38%) and autumn (32%).

Predisposing conditions were involved in 26 episodes (77%). The most common predisposing factors were remote head injury (17 [53%] of 32 episodes) and CSF leakage (9 [32%] of 28 episodes); 6 episodes involved both of these predisposing factors. Of the 17 episodes involving remote head injury, 15 (88%) occurred in men. In the 3 patients with CSF leakage who did not experience previous trauma, 2 had undergone surgical procedures involving the dura mater, and in 1 patient, the cause was unidentifiable. An immunocompromised state was involved in only 3 (9%) of 34 episodes; 1 of these episodes

was in a patient who was HIV positive, 1 in a patient who had a splenectomy, and 1 in a patient who was known to have alcoholism.

At presentation, symptoms were present for <24 h for 21 (58%) of 30 episodes. Most patients presented with classic symptoms and signs of bacterial meningitis (table 1); however, the triad of neck stiffness, fever, and altered mental status was present in patients only for 11 (32%) of 34 episodes. For 6 (18%) of 34 episodes, the patients presented with a Glasgow Coma Score of ≤ 8 , indicating coma. For 4 (12%) of 34 episodes, rhinorrhoea (nasal CSF leakage) was reported at hospital admission.

CT of the brain was performed at hospital admission for 27 (79%) of 34 episodes and revealed the potential causes of recurrent meningitis that were involved in 6 episodes (22%). Overall, CT abnormalities were found for 16 of these 27 episodes (67%) and consisted of posttraumatic abnormalities for 5 episodes, cerebral edema for 3, hydrocephalus and brain infarction for 2; sinusitis, mastoiditis, and pneumatocephalus each were involved in 1 episode. Posttraumatic abnormalities included localized posttraumatic brain atrophy in 4 patients and skull fractures in 2 (1 patient had both abnormalities on CT). Congenital malformations were not reported.

Cranial CT was performed before lumbar puncture for 12 (44%) of 27 episodes; antimicrobial therapy was started before CT for only 3 (25%) of these episodes. At hospital admission, cranial CT was repeated for 10 (37%) of 27 episodes. New abnormalities were found to be involved in 5 episodes, including cerebral edema and cerebral infarctions in 2 episodes each and a subarachnoid hemorrhage in 1 episode. MRI was performed at hospital admission for 1 patient and revealed a defect of the cribriform plate and accumulation of CSF in the nasal cavity.

Lumbar puncture was performed for all episodes. Opening pressure was recorded for 13 (38%) of 34 episodes and revealed a median pressure of 370 mm of water. At least 1 individual CSF finding that was indicative 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) [13] was found for 28 (88%) of 32 evaluated episodes. Gram staining of CSF samples was performed for 31 (91%) of 34 episodes and correctly identified the causative microorganism involved in 25 episodes; for 6 episodes, Gram staining revealed no microorganisms.

The causative microorganisms, as identified by CSF culture, were *S. pneumoniae* in 28 (85%) of 34 episodes, *Haemophilus influenzae* in 3 (9%), *N. meningitidis* in 2 (6%), and *Staphylococcus aureus* in 1 (3%). This last episode occurred in a patient who had CSF leakage under the facial skin. The causative bacterial species of the previous episode of meningitis was known

Table 1. Clinical characteristics and laboratory findings at hospital admission for 31 patients who experienced 34 episodes of recurrent community-acquired meningitis.

Variable	Value
Mean age, years (range)	43 (17–83)
Male sex	25/34 (74)
Duration of symptoms, <24 h	19/30 (63)
Seizures	6/32 (19)
Previously treated with antimicrobials	2/34 (6)
Predisposing factors	26/34 (77)
Immunocompromise	3/34 (9)
Pneumonia	4/34 (12)
Otitis or sinusitis	4/34 (12)
Remote neurosurgical procedure	3/27 (11)
Remote head trauma	13/32 (41)
History of CSF leakage	9/28 (32)
Symptoms on presentation	
Headache	28/31 (90)
Nausea	25/30 (83)
Neck stiffness	25/32 (78)
Temperature, ≥38°C	25/31 (81)
Score on Glasgow Coma Scale ^a	
Median ± SD	12 ± 3
≤14	24/34 (71)
≤8	6/34 (18)
Triad of fever, neck stiffness, and change in mental status	11/34 (32)
Focal neurological deficits	10/34 (30)
Cranial nerve palsy	8/34 (24)
Index of CSF inflammation ^b	
WBC count	
Median cells/mm ³ (range)	3467 (0–56320)
<100 cells/mm ³	3/30 (10)
100–999 cells/mm ³	2/30 (7)
>999 cells/mm ³	25/30 (83)
Protein concentration, median g/L (range)	2.57 (0.37–9.15)
Median CSF glucose concentration: blood glucose concentration (range)	0.24 (0.0–1.0)
CSF Gram stain results	
Negative	6/31 (19)
Gram-positive cocci	23/31 (74)
Gram-negative cocci	2/31 (6)
Causative organism	
<i>Streptococcus pneumoniae</i>	28/34 (85)
<i>Haemophilus influenzae</i>	3/34 (9)
<i>Neisseria meningitidis</i>	2/34 (6)
<i>Staphylococcus aureus</i>	1/34 (3)
Blood chemical test result ^c	
ESR, median mm/h (range)	13 (1–112)
C-reactive protein concentration, median mg/L (range)	104 (4–286)
Thrombocyte count, median 10 ⁹ cells/L (range)	221 (53–350)

NOTE. Data are no. (%) of episodes, unless otherwise indicated. ESR, erythrocyte sedimentation rate.

^a A score ≤14 indicates a change in mental status, and a score ≤8 indicates coma.

^b CSF pressure was measured during 13 episodes, CSF WBC count was determined during 30 episodes, CSF protein concentration was measured during 26 episodes, and CSF glucose concentration: blood glucose concentration was determined during 27 episodes.

^c ESR was determined during 26 episodes, C-reactive protein concentration was determined during 18 episodes, and thrombocyte count was determined during 31 episodes.

for 12 episodes and was similar to the causative bacterial species of the current episode for 11 episodes (92%). *S. pneumoniae* was the causative microorganism of meningitis in all 3 immunocompromised patients.

The causative bacterial species in the patient who had 6 episodes of bacterial meningitis were *S. pneumoniae* (episodes 1 and 2), group A streptococci (episode 4), and *N. meningitidis* (episode 5 and 6); CSF culture results were negative during episode 3. One additional patient experienced 2 episodes of meningococcal meningitis during the study period.

The distribution of serotypes of *S. pneumoniae* was type 14 in 5 (18%) episodes; types 6B and 35F in 6 (11%) episodes each; types 6A, 9V, 10A, 16F, and 22F in 10 (7%) episodes each; types 3, 4, 15C, 19A, 22F, and 23F in 6 (4%) episodes each, and unknown in 1 episode. The causative organism was one of the serotypes included in the 7-valent conjugated vaccine in only 13 episodes (46%); the coverage of the 23-valent pneumococcal polysaccharide vaccine was 61%.

Initial antimicrobial treatment consisted of penicillin or amoxicillin for 17 (50%) of 34 episodes, a third-generation cephalosporin for 12 (35%) episodes, and a combination of amoxicillin and third-generation cephalosporin for 1 (3%) episode; other regimens were used for 4 episodes (12%). Data on antimicrobial therapy were missing for 1 episode. Initial therapy was microbiologically adequate for all evaluated episodes. Adjunctive steroids were administered to 2 patients after clinical deterioration during the clinical course. One patient was included in the European Dexamethasone Study and was randomized to the placebo group [14].

During the clinical course, neurologic complications occurred during 23 (67%) of 34 episodes, and systemic complications developed during 6 (18%) of 34 episodes (table 2). The outcome was death for 5 (16%) of 31 patients; 1 additional patient had a suboptimal score on the Glasgow Outcome Scale (score, 4). One patient with pneumococcal meningitis died of subarachnoid hemorrhage. Neurological examination was performed at hospital discharge for all surviving patients. New neurological sequelae were found in 2 patients and consisted of hearing impairment and sixth cranial nerve palsy.

The vaccination status of many patients was unknown. Two patients were vaccinated with the 23-valent pneumococcal vaccine (pneumovax-23) after a second episode of pneumococcal meningitis. Both patients experienced recurrence of pneumococcal meningitis despite vaccination. Two patients experienced recurrent meningococcal meningitis, 1 of whom was vaccinated with an unknown meningococcal vaccine after the first episode of meningococcal meningitis (i.e., the patient's fifth episode of meningitis). Despite this vaccination, a recurrence of meningococcal meningitis occurred, which was the patient's sixth episode of bacterial meningitis.

Table 2. Complications during hospital admission and outcome of recurrent bacterial meningitis

Complication or outcome	No. (%) of episodes
Seizures	7/34 (21)
Cardiorespiratory failure	6/34 (18)
Required mechanical ventilation	5/34 (15)
Sepsis	3/34 (9)
Hyponatremia	6/32 (18)
Fever ^a	
Recurrent	6/34 (18)
Persistent	1/34 (21)
Impaired consciousness	16/34 (47)
Hemiparesis	1/34 (3)
Hearing impairment	2/34 (6)
Pneumonia	1/16 (6)
Score on the Glasgow Outcome Scale ^b	
1	5/34 (15)
2	0/34
3	0/34
4	1/34 (3)
5	27/34 (82)
Sequelae at discharge	
Focal cerebral deficit	0/34
Cranial nerve palsy ^c	2/34 (6)

^a Recurrent fever was defined as fever reoccurring after at least 1 afebrile day, and persistent fever was defined as a temperature $\geq 38^{\circ}\text{C}$ for >10 days after the initiation of appropriate antimicrobial treatment.

^b A score of 1 indicated death, 2 indicated a vegetative state, 3 indicated severe disability, 4 indicated moderate disability, and 5 indicated mild or no disability.

^c Hearing impairment and sixth cranial nerve palsy each occurred during 1 episode.

DISCUSSION

Our study reveals that recurrent bacterial meningitis occurs in 5% of community-acquired bacterial meningitis episodes. This frequency is somewhat lower than that found in a retrospective study evaluating 275 patients with community-acquired bacterial meningitis in a tertiary referral center [2]. In this case series, 33 (11%) of 296 episodes occurred in patients who had ≥ 2 episodes of community-acquired meningitis [2]. Our prospective study was performed nationwide and carefully excluded cases of nosocomial meningitis; therefore, our study provides an accurate estimate of the incidence of community-acquired recurrent bacterial meningitis.

Most patients with recurrent meningitis had predisposing conditions. Common predisposing conditions in our series were remote head injury (in 53% of episodes) and CSF leakage (in 38% of episodes); only a small minority of patients had an impaired humoral immunity. This is comparable to the previously mentioned retrospective study, which reported a remote history of head trauma or neurosurgical procedures in 47% of patients with recurrent meningitis. Although overt CSF leak-

age was seldom present at presentation, anatomical defects after head trauma can be regarded as the principal pathophysiological mechanism leading to recurrent bacterial meningitis and may have delayed onset until years after trauma [5, 6, 8].

The predominant causative organism was *S. pneumoniae*. This bacterium is a frequent cause of nonrecurrent community-acquired bacterial meningitis and is a part of the normal nasopharyngeal flora. The predominance of *S. pneumoniae* as a cause of recurrent meningitis has been reported previously [1–3].

An interesting finding is that 75% of the patients were male. The male-to-female ratio in the whole group of patients with community-acquired pneumococcal meningitis was 50:50 [15]. One explanation for the predominance of male sex among patients having recurrent meningitis is that head trauma is more likely to occur in male individuals than in female individuals. A recent Dutch prospective multicenter study evaluating minor head injury revealed a male predominance of 71% [16]. Remote head injury is an important predisposing condition for recurrent community-acquired bacterial meningitis. However, there might be other unidentified factors as well. A recent study revealed that male sex is an individual risk factor for developing meningitis after a craniotomy, although most patients had staphylococcal meningitis [17].

Two patients (6%) had recurrent meningitis caused by *N. meningitidis*. One of these patients experienced 6 episodes involving different causative organisms and CSF leakage; the previous causative organism was unknown for the other patient. In the literature, recurrent meningococcal meningitis is frequently associated with complement deficiencies [18–20]. The recurrence of meningococcal meningitis occurs in ~45% of patients with a complement deficiency [20]. However, *N. meningitidis* is a pharyngeal commensal in 9% of the population [18]; therefore, meningococcal meningitis is also possible when CSF leakage is the predisposing condition.

The mortality rate was substantial (15%) but much lower than that for nonrecurrent pneumococcal meningitis (34%) [12]. This difference in mortality rate might be explained by early symptom recognition by patients and their families, because they may recognize symptoms of previous episodes. This may also explain the relatively high proportion of patients presenting after having symptoms for <24 h and the low proportion of patients having the triad of neck stiffness, fever, and altered mental status. Another explanation might be competing risks between mortality and recurrence of illness; there is no recurrence of meningitis when a patient has died.

Our study has several important limitations. First, only patients who had a positive CSF culture result were included. Negative CSF culture results occur among 11%–30% of patients with bacterial meningitis [2, 12]. However, the clinical presentation in patients with positive and negative CSF culture results

was closely similar in several studies [2, 4]. Furthermore, patients with space-occupying lesions on CT, such as hemorrhages, associated with the infection may not undergo lumbar puncture [12]. For patients with coagulation disorders or severe septic shock, lumbar puncture might be postponed, which can result in negative CSF culture results, as well [12]. Therefore, these patient groups were probably only partly represented in our study, which might have caused an underestimation of the mortality rate. Finally, patients were not routinely tested for complement deficiency; this was an observational cohort study.

In patients with no apparent cause of recurrent meningitis or known history of head trauma, the high prevalence of remote head injury and CSF leakage in our series justifies an active search for anatomical defects and CSF leakage in patients with recurrent bacterial meningitis [8–11]. Detection of β -2-transferrine in nasal discharge in cases of rhinorrhoea is a sensitive and specific method to confirm the presence of a CSF leak [21–23]. Optimum imaging is performed using thin-slice CT of the skull base and is the initial imaging of choice [5, 9, 24]. It is important to take into account that small bone defects on CT do not prove CSF leakage [24]. T2-weighted MRI may detect a small CSF leak but lacks fine bone detail [25, 26]. Because CSF leaks are often intermittent, the administration of intrathecal contrast will not be more accurate to prove leakage and depends on the timing of imaging [24, 27]. Anatomical defects and CSF leakage might require the consultation of a neurosurgeon or otolaryngologist to evaluate the necessity of surgical repair, which has an overall high success rate and low mortality and morbidity [8, 24, 28]. In patients with recurrent meningococcal meningitis, it depends on the patient's history whether a complement or immunoglobulin deficiency should be excluded before a search for anatomical defects and CSF leakage is initiated [18–20].

The vaccination status was largely unknown in our series, which is an important shortcoming of our study. Only 2 patients in our study were known to be vaccinated after recurrent episodes of meningitis. In previous literature, the role of vaccination to prevent recurrence of meningitis was only investigated in patients with meningococcal infection caused by complement or immunoglobulin deficiency or after splenectomy [19, 29]. This group of patients and their possible affected family members should be vaccinated to prevent meningitis [19]. Both vaccinated patients in our study experienced recurrence after vaccination; however, vaccination should be routine for patients with persistent CSF leakage. The efficacy of prophylactic antibiotics in patients with CSF leakage remains controversial in the literature [5, 6, 17, 30, 31].

We conclude that most patients with recurrent meningitis are male individuals with predisposing conditions, which, in most cases, are remote head injury or CSF leakage. The high prevalence of remote head injury and CSF leakage in our series

justifies an active search for anatomical defects and CSF leakage in a patient with recurrent bacterial meningitis.

Acknowledgments

We thank the many physicians in The Netherlands for their cooperation.

Financial support. The Netherlands Organization for Health Research and Development (NWO-Veni grant 2006 [916.76.023] and NWO-Rubicon grant 2006 [019.2006.1310.0001] to D.v.d.B.). The Dutch Meningitis Cohort Study was supported in part by a research grant from Roche Pharmaceuticals.

Potential conflicts of interest. All authors: no conflicts.

References

1. van de Beek D, de Gans J, Tunkel AR, Wijdicks EF. Community-acquired bacterial meningitis in adults. *N Engl J Med* **2006**; 354:44–53.
2. Durand ML, Calderwood SB, Weber DJ, et al. Acute bacterial meningitis in adults: a review of 493 episodes. *N Engl J Med* **1993**; 328: 21–8.
3. Schlech WF III, Ward JI, Band JD, Hightower A, Fraser DW, Broome CV. Bacterial meningitis in the United States, 1978 through 1981. The National Bacterial Meningitis Surveillance Study. *JAMA* **1985**; 253: 1749–54.
4. Sigurdardottir B, Bjornsson OM, Jonsdottir KE, Erlendsdottir H, Gudmundsson S. Acute bacterial meningitis in adults: a 20-year overview. *Arch Intern Med* **1997**; 157:425–30.
5. Pappas DG, Hammerschlag PE, Hammerschlag M. Cerebrospinal fluid rhinorrhea and recurrent meningitis. *Clin Infect Dis* **1993**; 17:364–8.
6. Choi D, Spann R. Traumatic cerebrospinal fluid leakage: risk factors and the use of prophylactic antibiotics. *Br J Neurosurg* **1996**; 10:571–5.
7. Whittet HB, Barker S, Anslow P, Leighton S. Heterotopic brain tissue: a rare cause of adult recurrent meningitis. *J Laryngol Otol* **1990**; 104: 328–30.
8. Giunta G, Piazza I. Recurrent bacterial meningitis occurring five years after closed head injury and caused by an intranasal post-traumatic meningo-encephalocele. *Postgrad Med J* **1991**; 67:377–9.
9. Carrol ED, Latif AH, Misbah SA, et al. Recurrent bacterial meningitis: the need for sensitive imaging. *BMJ* **2001**; 323:501–3.
10. Ford H, Wright J. Recurrent bacterial meningitis in adults: a case series. *J Infect* **1996**; 33:131–3.
11. Hoşoğlu S, Ayaz C, Cevic A, Çümen B, Geyik MF, Kökoğlu ÖF. Recurrent bacterial meningitis: a six year experience in adult patients. *J Infect* **1997**; 35:55–62.
12. van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis. *N Engl J Med* **2004**; 351:1849–59.
13. Spanos A, Harrell FE Jr, Durack DT. Differential diagnosis of acute meningitis: an analysis of the predictive value of initial observations. *JAMA* **1989**; 262:2700–7.
14. de Gans J, van de Beek D; European Dexamethasone in Adulthood Bacterial Meningitis Study Investigators. Dexamethasone in adults with bacterial meningitis. *N Eng J Med* **2002**; 347:1549–56.
15. Weisfelt M, van de Beek D, Spanjaard L, Reitsma JB, de Gans J. Clinical features, complications, and outcome in adults with pneumococcal meningitis: a prospective case series. *Lancet Neurol* **2006**; 5:123–9.
16. Smits M, Dippel DW, de Haan GG, et al. External validation of the Canadian CT head rule and the New Orleans criteria for CT scanning in patients with minor head injury. *JAMA* **2005**; 294:1519–25.
17. Korinek AM, Baugnon T, Golmard JL, van Effenterre R, Coriat P, Puybasset L. Risk factors for adult nosocomial meningitis after craniotomy: role of antibiotic prophylaxis. *Neurosurgery* **2006**; 59:126–33; discussion 126–33.
18. Swart AG, Fijen CAP, te Bulte MT, Daha MR, Dankert J, Kuijper EJ. Prevalence in The Netherlands of complement deficiency in patients having experienced a meningococcal infection. *Ned Tijdschr Geneesk* **1993**; 137:1147–52.
19. Stephens D, Hajjeh R, Baughman W, Harvey R, Wenger J, Farley M. Sporadic meningococcal disease in adults: results of a 5-year population-based study. *Ann Intern Med* **1995**; 123:937–40.
20. Andreoni J, Kayhty H, Densen P. Vaccination and the role of capsular polysaccharide antibody in prevention of recurrent meningococcal disease in late complement component-deficient individuals. *J Infect Dis* **1993**; 168:227–31.
21. Nandapalan V, Watson ID, Swift AC. Beta-2-transferrin and cerebrospinal fluid rhinorrhoea. *Clin Otolaryngol* **1996**; 21:259–64.
22. Ryall RG, Peacock MK, Simpson DA. Usefulness of beta-2-transferrin assay in the detection of cerebrospinal fluid leaks following head injury. *J Neurosurg* **1992**; 77:737–9.
23. Bateman N, Jones NS. Rhinorrhoea feigning cerebrospinal fluid leak: nine illustrative cases. *J Laryngol Otol* **2000**; 114:462–4.
24. Lund VJ, Lloid S, Lloyd G, et al. Optimum imaging and diagnosis of cerebrospinal fluid rhinorrhoea. *J Laryngol Otol* **2000**; 114:988–92.
25. Stafford Johnson DB, Brennan P, Toland J, O'Dwyer AJ. Magnetic resonance imaging in the evaluation of cerebrospinal fluid fistulae. *Clin Radiol* **1996**; 51:837–41.
26. Gupta V, Goyal M, Mishra NK, Sharma A, Gaikwad SB. Positional MRI: a technique for confirming the site of leakage in cerebrospinal fluid rhinorrhoea. *Neuroradiology* **1997**; 39:818–20.
27. Stone JA, Castillo M, Neelon B, Mukherji SK. Evaluation of CSF leaks: high-resolution CT compared with contrast-enhanced CT and radio-nuclide cisternography. *Am J Neuroradiol* **1999**; 20:706–12.
28. Friedman JA, Ebersold MJ, Quast LM. Post-traumatic cerebrospinal fluid leakage. *World J Surg* **2001**; 25:1062–6.
29. Omlin A, Muhlemann K, Fey M, et al. Pneumococcal vaccination in splenectomised cancer patients. *Eur J Cancer* **2005**; 41:1731–4.
30. Brody HA. Prophylactic antibiotics for posttraumatic cerebrospinal fluid fistulae, a meta-analysis. *Arch Otolaryngol Head Neck Surg* **1997**; 123:749–52.
31. Villalobos T, Arango C, Kubilis P, Rathore M. Antibiotics after basilar skull fractures: a meta-analysis. *Clin Infect Dis* **1998**; 27:364–9.