**Bacterial Meningitis 1**

**Dilemmas in the diagnosis of acute community-acquired bacterial meningitis**

Matthijs C Brouwer, Guy E Thwaites, Allan R Tunkel, Diederik van de Beek

Rapid diagnosis and treatment of acute community-acquired bacterial meningitis reduces mortality and neurological sequelae, but can be delayed by atypical presentation, assessment of lumbar puncture safety, and poor sensitivity of standard diagnostic microbiology. Thus, diagnostic dilemmas are common in patients with suspected acute community-acquired bacterial meningitis. History and physical examination alone are sometimes not sufficient to confirm or exclude the diagnosis. Lumbar puncture is an essential investigation, but can be delayed by brain imaging. Results of cerebrospinal fluid (CSF) examination should be interpreted carefully, because CSF abnormalities vary according to the cause, patient's age and immune status, and previous treatment. Diagnostic prediction models that use a combination of clinical findings, with or without test results, can help to distinguish acute bacterial meningitis from other causes, but these models are not infallible. We review the dilemmas in the diagnosis of acute community-acquired bacterial meningitis, and focus on the roles of clinical assessment and CSF examination.

**Introduction**

Acute community-acquired bacterial meningitis is a medical emergency, and patients with this disease need immediate medical assessment and treatment. Dilemmas exist in the diagnosis of patients with bacterial meningitis, because clinical findings do not always accurately identify patients with meningitis, and cerebrospinal fluid (CSF) analysis is not always diagnostic. Furthermore, in resource-poor countries with high rates of tuberculosis and HIV, and poor laboratory diagnostics, establishment of the diagnosis of bacterial meningitis can be even more difficult. In this review, we focus on dilemmas in the diagnosis of acute community-acquired bacterial meningitis in children and adults; diagnostic dilemmas in patients with nosocomial bacterial meningitis have been reviewed previously. We review the clinical presentation and differential diagnosis of the disease, use of lumbar puncture, and interpretation of CSF results, and draw attention to advances in diagnostic markers and the use of prediction models in the diagnosis of acute community-acquired bacterial meningitis after the neonatal period.

**Clinical presentation**

In view of the urgent need for antibiotic administration in patients with acute community-acquired bacterial meningitis, early recognition of the disease is essential. The sequence and development of signs and symptoms before hospital admission were retrospectively assessed in 448 children and adolescents with meningococcal diseases, encompassing the full range of disease from sepsis to meningitis. Although limited by its retrospective design, this study showed that the classic symptoms of rash, neck stiffness, and impaired consciousness do not develop until late in the pre-hospital illness, if at all. Adults also displayed this absence of classic symptoms. In a prospective nationwide cohort of 696 adults with culture-proven acute bacterial meningitis, the classic triad of fever, neck stiffness, and altered mental status was present in only 44% of episodes; however, 95% of episodes were characterised by at least two of the four symptoms of headache, fever, neck stiffness, and altered mental status.

Investigators of several studies have assessed the usefulness of neck stiffness, Kernig’s sign, and Brudzinski’s sign for the diagnosis of community-acquired bacterial meningitis. A meta-analysis of prospective studies in children with suspected bacterial meningitis showed sensitivities of 51% for neck stiffness, 53% for Kernig’s sign (likelihood ratio positive test [LR+] 3.5, 95% CI 2.10–5.70; LR negative test [LR−] 0.56, 0.41–0.75), and 66% for Brudzinski’s sign (LR+ 2.5, 95% CI 1.80–3.60; LR− 0.46, 0.31–0.68) for the diagnosis of bacterial meningitis. In adults, these clinical findings have low diagnostic accuracy for prediction of CSF pleocytosis (table 1), suggesting that absence of these findings...
cannot be used to exclude the possibility of bacterial meningitis. Physicians should not rely on one test for the diagnosis of bacterial meningitis; the patient’s history and physical examination findings should be used together to create a clinical impression that leads to selection of appropriate diagnostic studies.

Many patients with bacterial meningitis have predisposing disorders. Ear, sinus, or lung infections precede pneumococcal meningitis in 40% of patients. Endocarditis is a rare predisposing infection in patients with bacterial meningitis, but can coexist in those with *Staphylococcus aureus* or *Streptococcus pneumoniae* meningitis. Patients with acute bacterial meningitis can also present with signs of septic shock (10–25% of cases), especially those with meningococcal meningitis. In these patients, meningitis can initially be overlooked because changed mental status is attributed to hypovolaemic shock or septic encephalopathy.

**Differential diagnosis**

The differential diagnosis of the triad of fever, headache, and stiff neck includes bacterial or viral meningitis, fungal meningitis, tuberculous meningitis, drug-induced meningitis, carcinomatous or lymphomatous meningitis, meningitis associated with inflammatory diseases (eg, systemic lupus erythematosus, sarcoidosis, Behçet’s disease, or Sjögren’s syndrome), cerebral abscess, and subarachnoid haemorrhage (when the body temperature is normal or only moderately raised and the onset of headache is acute). The relative importance of these disorders can be measured by a careful neurological examination and a thorough patient history, including information about medical history, recent travel, vaccinations, the use of illicit and immunosuppressive drugs, and risk factors for HIV and sexually transmitted infections. Furthermore, the local epidemiology of rare microorganisms causing CNS infection, such as amoebae, *Trypanosoma cruzi*, *Leptospira* spp, and *Rickettsia* spp, should be considered. Patients with immunosuppression, especially those with HIV infection, have an increased risk of pneumococcal, tuberculous, and cryptococcal meningitis. In resource-poor settings where tuberculosis and acute bacterial meningitis are both endemic, a duration of symptoms of more than 5 days before presentation predicts a diagnosis of tuberculous meningitis. Discrimination of bacterial from tuberculous meningitis is crucial, because death or severe neurological disability from tuberculous meningitis is strongly associated with delays in initiation of antituberculosis chemotherapy. If patients have a history of cancer, leukaemia, lymphoma, or autoimmune diseases, physicians should include in the differential diagnosis meningeal or cerebral localisation of these diseases. If no specific risk factors are present, viral meningitis (eg, caused by enteroviruses, herpes simplex virus type 2, or mumps virus) is the most common diagnosis. The clinical distinction between viral and acute bacterial meningitis is difficult in the acute phase of illness; therefore, some of these patients are admitted to the hospital and treated with antibiotics until CSF culture results are available or the diagnosis of viral meningitis has been confirmed.

**Lumbar puncture**

Because of the urgent and essential need for a lumbar puncture to obtain CSF for diagnostic studies, physicians need to establish whether cranial imaging is needed before doing a lumbar puncture to minimise the potential risks of this procedure. Patients with space-occupying intracranial lesions can present with symptoms identical to acute community-acquired bacterial meningitis or these lesions can complicate acute bacterial meningitis early in the disease course (eg, subdural empyema, epidural abscess, brain abscess, cerebral infarctions, or obstructive hydrocephalus; figure 1); in these patients, brain herniation can complicate lumbar puncture. Withdrawal of CSF at the lumbar point causes a cranial–caudal pressure gradient, with the potential to increase the existing brain shift caused by a space-occupying lesion. The incidence of brain herniation after lumbar puncture in patients with meningitis has been debated. Investigators of retrospective cohort studies from the USA and the UK reported a cerebral herniation rate after lumbar puncture proven by post-mortem examination in two (1%) of 252 children with meningococcal meningitis and five (1%) of 439 adults with bacterial meningitis. However, cerebral herniation also occurs in patients with acute bacterial meningitis without lumbar puncture, which complicates this dilemma further.
Physicians can use cranial imaging to help to identify patients at risk of brain herniation after lumbar puncture, but this method is associated with delayed therapy and increased mortality.21,31,32 A retrospective Canadian study of 123 patients showed that a substantial delay of more than 6 h in initiation of antibiotic treatment occurred in 15 (63%) of 24 adult patients in whom cranial CT was done before the lumbar puncture.32 Therefore, empirical treatment should always be started before the patient is sent for brain imaging.

To avoid diagnostic delays, conserve resources, and reduce radiation exposure and unnecessary treatment, clinical examination can be used to select patients who need CT before lumbar puncture.21 In a prospective study of 301 adults with suspected acute bacterial meningitis, 235 patients had a CT scan before lumbar puncture. Abnormalities were identified in 52 (24%) patients, and lesions causing brain shift in 11 (5%).21 New-onset seizures, an immunocompromised state (patients with HIV/AIDS, those receiving immuno-suppressive therapy, or those who have undergone transplantation), history of a CNS lesion (mass lesion, stroke, or focal infection), signs that suggest space-occupying lesions (papilloedema, focal neurological deficits, or evolving signs of brain tissue shift), or moderate-to-severe impairment of consciousness can predict brain imaging abnormalities and can therefore be used to identify patients with suspected acute bacterial meningitis who need imaging before lumbar puncture.3,12 When none of these risk factors is present in adults, brain imaging before the lumbar puncture is not needed. Although studies of the selection of children with suspected acute bacterial meningitis who need imaging before lumbar puncture are scarce, criteria similar to those in adults have been recommended.28 A normal CT scan on admission does not exclude the possibility that the patient will develop brain herniation during the meningitis episode. Other contraindications for doing a lumbar puncture are coagulation disorders such as disseminated intravascular coagulation, use of anticoagulant drugs, or significant thrombocytopenia in patients receiving chemotherapy or those with haematological diseases.33,34 If a patient presents with septic shock or respiratory failure, the lumbar puncture should be postponed until the patient has been stabilised.

In settings with a high HIV seroprevalence, many patients with suspected acute community-acquired bacterial meningitis would qualify for cranial imaging before lumbar puncture because of the high likelihood of HIV infection,35–37 yet CT equipment can be scarce in these settings.38 The risk of death resulting from an inaccurate diagnosis through lumbar puncture deferral is considered greater than the risks that are associated with the procedure, irrespective of focal signs or a reduced state of consciousness, and therefore lumbar puncture should not be deferred.38

**CSF examination**

CSF examination is essential to establish the diagnosis of bacterial meningitis, identify the causative organism, and undertake in-vitro antibiotic susceptibility testing. Characteristic CSF findings for acute community-acquired bacterial meningitis are a polymorphonuclear pleocytosis, hypoglycorrhachia, and raised CSF protein concentrations.3,34,39,40 More than 90% of cases of acute bacterial meningitis present with a CSF white cell count of more than 100 cells per μL.3 In immunocompromised patients, CSF white cell counts are often low, although an acellular CSF is rare, except in patients with tuberculous meningitis.14,19 Polymorphonuclear cells can predominate in the acute phase of many other meningeal infections, including those caused by viruses and *Mycobacterium tuberculosis*, although, unlike in untreated acute bacterial meningitis, they rarely exceed 80% of the total white blood cell counts.3,34 CSF protein concentrations are
raised in 90% of patients with acute community-acquired bacterial meningitis.3,30,40,42,43

CSF culture is the gold standard for diagnosis of bacterial meningitis and is positive in 80–90% of patients with acute community-acquired bacterial meningitis before the start of treatment.39 CSF Gram staining is a rapid, inexpensive, and well validated method to assess the presence of bacteria in CSF (figure 2); the reported yield of CSF Gram staining in both children and adults ranges from 69% to 93% in pneumococcal meningitis and from 30% to 89% in meningococcal meningitis.39 The specificity of the CSF Gram stain was 97% in a cohort study including 696 adults with culture-proven acute bacterial meningitis.3 Blood cultures should always be done on admission and are especially helpful in patients in whom antibiotics are started before the lumbar puncture is undertaken, including when cranial CT is indicated.38 Blood cultures identify the causative organism in 50–80% of paediatric and adult cases.39 The yield of blood cultures decreases by 20% if the patient has been pretreated with antibiotics.44,45

Because CSF Gram stain and culture do not always identify the causative agent in all patients with bacterial meningitis, molecular diagnostic methods have been studied. Nucleic acid amplification tests, such as PCR, have proven their incremental value compared with Gram stain and CSF culture to identify the causative microorganism, especially in patients with acute community-acquired bacterial meningitis who received antibiotic treatment before lumbar puncture.39 PCR facilitated diagnosis in 33% of 409 patients aged between 1 month and 67 years in Burkina Faso who could not be diagnosed with conventional methods.46 Broad-range PCR can be used to detect the most common microorganisms in one test, and has adequate sensitivity and excellent specificity (table 2).47–50 PCR techniques have evolved rapidly and can now be done within 2 h in most

| Table 2: Test characteristics for multiplex CSF PCR in the diagnosis of bacterial meningitis |
|---------------------------------|------------------|------------------|------------------|------------------|
|                  | Number of patients (BM/controls) | Sensitivity | Specificity | PPV | NPV |
| **Corless:** CSF culture-confirmed cases (control samples: other bacteria or viruses) |
| Neisseria meningitidis | 32/0 | 89% | 100% | NA | NA |
| Streptococcus pneumoniae | 23/0 | 91% | 100% | NA | NA |
| Haemophilus influenzae | 6/0 | 100% | 100% | NA | NA |
| **Tzanakaki:** CSF culture-confirmed cases (control samples: other bacteria or viruses) |
| Neisseria meningitidis | 33/0 | 94% | 100% | 100% | 99.1% |
| Streptococcus pneumoniae | 26/0 | 88% | 100% | 100% | 99.1% |
| Haemophilus influenzae | 6/0 | 92% | 100% | 100% | 99.1% |
| **Parent du Châtelet:** CSF culture-confirmed cases (control samples: patients with negative cultures) |
| Neisseria meningitidis | 85/349 | 95% | 95% | NA | NA |
| Streptococcus pneumoniae | 16/418 | 79% | 95% | NA | NA |
| Haemophilus influenzae | 34/400 | 81% | 97% | NA | NA |
| **Sacchi:** CSF culture-confirmed cases (control samples: specimens positive for other pathogens) |
| Neisseria meningitidis | 90/51 | 100% | 100% | 98–100%* | 99–100%* |
| Streptococcus pneumoniae | 46/94 | 98% | 100% | 98–100%* | 99–100%* |
| Haemophilus influenzae | 3/139 | 67% | 100% | 98–100%* | 99–100%* |
| **Boving:** CSF culture-positive cases or Gram stain-positive cases (control samples: CSF culture-negative cases) |
| Neisseria meningitidis | 21/1166 | 91% | 99.1% | 68% | 100% |
| Streptococcus pneumoniae | 6/1181 | 100% | 99.7% | 67% | 100% |

BM=bacterial meningitis. PPV=positive predictive value. NPV=negative predictive value. CSF=cerebrospinal fluid. NA=not available. *Individual values per pathogen not presented.
industrialised countries; however, the availability of PCR in resource-poor settings is scarce.

An immunochromatographic test is available for the detection of *S pneumoniae* in CSF. In one study including 450 children with suspected acute bacterial meningitis, this test was 100% sensitive and specific for the diagnosis of pneumococcal meningitis; the overall sensitivity of this test ranges from 95% to 100%.32 Despite these promising results, more studies are needed to establish the usefulness of this test in non-specialist laboratories.

**Prediction models**

In patients without a positive CSF Gram stain or culture, the diagnosis of acute bacterial meningitis is often difficult to establish or reject. A combination of clinical findings with or without test results has been assessed to develop models that allow accurate prediction of the likelihood of acute bacterial meningitis compared with other possible causes (especially viral meningitis). Oostenbrink and colleagues33–35 developed a prediction model to guide decisions about the use of lumbar puncture and empirical antibiotic therapy in children aged between 29 days and 15 years with suspected acute bacterial meningitis. The model included assessment of variables from patients' history, physical examination, and measurement of serum C-reactive protein (table 3). In both the derivation and validation sets, none of the children with risk scores less than 9·5 had acute bacterial meningitis, and lumbar puncture could be withheld in about 35% of children with meningeal signs without a single case of acute bacterial meningitis being missed. In a follow-up study, the same investigators reported that the addition of CSF polymorphonuclear cell count and ratio of CSF to blood glucose to their diagnostic model was useful for the decision to start empirical antibiotic therapy in children with meningeal signs.34 These prediction models were subsequently analysed in an external population from four paediatric hospitals in the Netherlands.35 In the derivation part of the study, the investigators used a clinical score of 9·5 to discriminate between children with or without acute bacterial meningitis; however, application of this score to prospective validation yielded two children with acute bacterial meningitis with a clinical score of 8·5. Bacterial meningitis was diagnosed in none of the 205 children with a score less than 8·5, 13% with a score of 8·5–14·9, 52% with a score of 15–19·9, and 87% with a score greater than 20. The frequency of acute bacterial meningitis increased with the CSF score, although there was no threshold value at which the CSF score could be used to exclude a diagnosis of acute bacterial meningitis.

Other investigators have examined specific CSF variables to predict the likelihood of acute bacterial meningitis. In one analysis of the records of 422 immunocompetent patients older than 1 month with acute bacterial or viral meningitis,43 a CSF glucose concentration less than 1·9 mmol/L, a ratio of CSF to blood glucose less than 0·23, a CSF protein concentration above 2·2 g/L, and more than 2000 CSF leucocytes per μL, or more than 1180 CSF neutrophils per μL predicted bacterial rather than viral meningitis with 99% certainty or higher (table 3). This model was validated in a retrospective review of 160 adult patients with bacterial or viral meningitis,44 which showed that the model was robust when applied to a geographically distinct adult population. Further validation was achieved in another retrospective review of 500 consecutive cases of community-acquired meningitis in children older than 1 month and adults; when the probability of acute bacterial meningitis was equal to 0·1, the negative and positive predictive values of this model were 99% and 68%, respectively.45 These investigators also created a new model with four slightly different independent variables (CSF protein concentration, total CSF polymorphonuclear cell count, blood glucose concentration, and leucocyte count); the negative and positive predictive values of this model were 99% and 85%, respectively. When this model was used in patients younger than

<table>
<thead>
<tr>
<th>Studies</th>
<th>Population</th>
<th>Prediction rule</th>
<th>Scored items</th>
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<tbody>
<tr>
<td>Oostenbrink meningitis score</td>
<td>Oostenbrink (o/p, n=286; v=74),36</td>
<td>Children aged 1 month–15 years</td>
<td>Duration of complaints=1 point per day (maximum 10), vomiting=2, meningeal irritation=7, cyanosis=6, petechiae or ecchymosis=4, disturbed consciousness=8, CRP=0·5 points per 10 mg/L increase, CSF PMN count=0–4, CSF to blood glucose ratio=0–5 points per 0·1 decrease44</td>
</tr>
<tr>
<td>Oostenbrink meningitis score</td>
<td>Oostenbrink (o/r, n=227),37</td>
<td>Children aged 1 month–15 years</td>
<td>Duration of complaints=1 point per day (maximum 10), vomiting=2, meningeal irritation=7, cyanosis=6, petechiae or ecchymosis=4, disturbed consciousness=8, CRP=0·5 points per 10 mg/L increase, CSF PMN count=0–4, CSF to blood glucose ratio=0–5 points per 0·1 decrease44</td>
</tr>
<tr>
<td>Oostenbrink meningitis score</td>
<td>Oostenbrink (v/p, n=226)</td>
<td>Duration of complaints=1 point per day (maximum 10), vomiting=2, meningeal irritation=7, cyanosis=6, petechiae or ecchymosis=4, disturbed consciousness=8, CRP=0·5 points per 10 mg/L increase, CSF PMN count=0–4, CSF to blood glucose ratio=0–5 points per 0·1 decrease44</td>
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<tr>
<td>Bacterial meningitis score</td>
<td>Nigrovic (o/r, n=456, v=240),39</td>
<td>Children and young adults aged 29 days–18 years (16 years in Dubos study)</td>
<td>Duration of complaints=1 point per day (maximum 10), vomiting=2, meningeal irritation=7, cyanosis=6, petechiae or ecchymosis=4, disturbed consciousness=8, CRP=0·5 points per 10 mg/L increase, CSF PMN count=0–4, CSF to blood glucose ratio=0–5 points per 0·1 decrease44</td>
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<tr>
<td>Bacterial meningitis score</td>
<td>Dubos (v/r, n=198)</td>
<td>Children and young adults aged 29 days–18 years (16 years in Dubos study)</td>
<td>Duration of complaints=1 point per day (maximum 10), vomiting=2, meningeal irritation=7, cyanosis=6, petechiae or ecchymosis=4, disturbed consciousness=8, CRP=0·5 points per 10 mg/L increase, CSF PMN count=0–4, CSF to blood glucose ratio=0–5 points per 0·1 decrease44</td>
</tr>
<tr>
<td>Spansos CSF prediction model</td>
<td>Spansos (o/r, n=422),41</td>
<td>Children aged &gt;1 month and adults (in McKinney study, defined as &gt;17 years)</td>
<td>Duration of complaints=1 point per day (maximum 10), vomiting=2, meningeal irritation=7, cyanosis=6, petechiae or ecchymosis=4, disturbed consciousness=8, CRP=0·5 points per 10 mg/L increase, CSF PMN count=0–4, CSF to blood glucose ratio=0–5 points per 0·1 decrease44</td>
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<tr>
<td>Spansos CSF prediction model</td>
<td>McKinney (v/r, n=329)</td>
<td>Children aged &gt;1 month and adults (in McKinney study, defined as &gt;17 years)</td>
<td>Duration of complaints=1 point per day (maximum 10), vomiting=2, meningeal irritation=7, cyanosis=6, petechiae or ecchymosis=4, disturbed consciousness=8, CRP=0·5 points per 10 mg/L increase, CSF PMN count=0–4, CSF to blood glucose ratio=0–5 points per 0·1 decrease44</td>
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<tr>
<td>Spansos CSF prediction model</td>
<td>Hoogenboom (o/r, n=500),42</td>
<td>Children aged &gt;1 month and adults (in McKinney study, defined as &gt;17 years)</td>
<td>Duration of complaints=1 point per day (maximum 10), vomiting=2, meningeal irritation=7, cyanosis=6, petechiae or ecchymosis=4, disturbed consciousness=8, CRP=0·5 points per 10 mg/L increase, CSF PMN count=0–4, CSF to blood glucose ratio=0–5 points per 0·1 decrease44</td>
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<tr>
<td>Hoen CSF prediction model</td>
<td>Hoeken (o/r, n=500),43</td>
<td>Children aged &gt;1 month and adults (in McKinney study, defined as &gt;17 years)</td>
<td>Duration of complaints=1 point per day (maximum 10), vomiting=2, meningeal irritation=7, cyanosis=6, petechiae or ecchymosis=4, disturbed consciousness=8, CRP=0·5 points per 10 mg/L increase, CSF PMN count=0–4, CSF to blood glucose ratio=0–5 points per 0·1 decrease44</td>
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<tr>
<td>Hoen CSF prediction model</td>
<td>Baty (v/p, n=109)</td>
<td>Children aged &gt;1 month and adults (in McKinney study, defined as &gt;17 years)</td>
<td>Duration of complaints=1 point per day (maximum 10), vomiting=2, meningeal irritation=7, cyanosis=6, petechiae or ecchymosis=4, disturbed consciousness=8, CRP=0·5 points per 10 mg/L increase, CSF PMN count=0–4, CSF to blood glucose ratio=0–5 points per 0·1 decrease44</td>
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Table 3: Clinical prediction models for community-acquired acute bacterial meningitis

3–5 years, the positive and negative predictive values were 96% and 97%, respectively.

Other prediction models based on similar and other variables have also been developed and validated.56,62,63 Nigrovic and colleagues64 reviewed records of a cohort of 696 children and young adults aged between 29 days and 19 years diagnosed with meningitis. The investigators used multivariable logistic regression and recursive partitioning analyses to identify predictors from the derivation set, which led to development of a bacterial meningitis score (table 3) to distinguish bacterial from aseptic meningitis. Patients with none of these parameters were given a score of 0 and identified as low risk for acute bacterial meningitis, with a negative predictive value of 100% (95% CI 97–100) and a specificity of 73% (51–100). A score above 2 had a sensitivity of 87% (72–96) and a positive predictive value of 87% (72–96) for acute bacterial meningitis. These figures need to be interpreted with some caution, because the prediction model includes a positive CSF Gram stain that adds 2 points to the risk score. Patients with positive Gram stains, in whom there is no diagnostic uncertainty, should ideally be excluded from studies of prediction models to differentiate bacterial from viral meningitis. The investigators validated the score externally with a large retrospective cohort of 3295 patients aged between 29 days and 19 years diagnosed with meningitis. The investigators developed a new score using a C-reactive protein concentration less than 2·89 mmol/L. A score of 0 points distinguished viral meningitis from acute bacterial meningitis in 54 of 70 children (100% accuracy and 100% specificity); with this formula, only 16 patients with viral meningitis would have received antibiotics compared with the 41 patients in their series who were actually treated.65

Although another study66 has confirmed the usefulness of the Nigrovic bacterial meningitis score compared with other models, universal applications of bedside prediction models are not always appropriate. In a retrospective study of the application of the bacterial meningitis score to 21 children aged 0–15 years with acute bacterial meningitis, five did not fit all criteria and would have been considered low risk and not treated.67 These investigators developed a new score using a C-reactive protein concentration less than 20 mg/L, CSF glucose concentration above 2·89 mmol/L, and CSF protein concentration less than 1 g/L. A score of 0 points distinguished viral meningitis from acute bacterial meningitis in 54 of 70 children (100% accuracy and 100% specificity); with this formula, only 16 patients with viral meningitis would have received antibiotics compared with the 41 patients in their series who were actually treated.64

The benefit of these prediction models in patients with suspected acute bacterial meningitis is to guide decision making for those in whom further diagnostic studies and therapy could be appropriately withheld. In individual patients with suspected acute bacterial meningitis, a prediction model could have value, but clinicians’ judgment (to include the presence of other presenting symptoms, signs, and laboratory variables) should continue to be used in decisions about the need for CSF analysis and administration of empirical antibiotic and adjunctive therapy. The use of these models should also be limited to the age cohort in which they were developed. Another important limitation of the described prediction models is that they all differentiate between viral and acute bacterial meningitis, but in clinical practice many other causes (eg, fungal or mycobacterial meningitis) might need to be considered. These prediction models might be most useful in doubtful cases, when they can be used to suggest a reconsideration of the diagnosis.

### Diagnostic markers

Studies have examined other markers for their diagnostic use in patients with acute bacterial meningitis (table 4); these studies have focused mainly on the differentiation of acute bacterial from viral meningitis. Determination of the CSF lactate concentration is a widely available, straightforward, cheap, and rapid diagnostic test.71,72 Two meta-analyses, one including 25 studies with 1692 patients (adults and children)73 and the other including 31 studies with 1885 patients (adults and children),74 both concluded that the diagnostic accuracy of CSF lactate is better than that of CSF white blood cell

<table>
<thead>
<tr>
<th>CSF analytes</th>
<th>Number of patients (BM/AM/HC)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
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<tr>
<td>Complement factor 3</td>
<td>18/21/64</td>
<td>100%</td>
<td>100%</td>
<td>94.7%</td>
<td>100%</td>
</tr>
<tr>
<td>Complement factor B</td>
<td>18/21/64</td>
<td>100%</td>
<td>92.5%</td>
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<td>Linder(7) (A)</td>
<td>3/7/9/97</td>
<td>100%</td>
<td>99.2%</td>
<td>96.2%</td>
<td>100%</td>
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<td>Heparin-binding protein</td>
<td>47/17/72</td>
<td>100%</td>
<td>82%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Holub(67) (A)</td>
<td>92/89/9</td>
<td>73%</td>
<td>77%</td>
<td>94%</td>
<td>34%</td>
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<td>Cortisol</td>
<td>23/26/95</td>
<td>78%</td>
<td>96%</td>
<td>95%</td>
<td>83%</td>
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<td>Dettermann(5) (A)</td>
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<td>74%</td>
<td>81%</td>
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<td>78%</td>
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<td>Interleukin 1β</td>
<td>12/41/42</td>
<td>96%</td>
<td>51%</td>
<td>19%</td>
<td>98%</td>
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<tr>
<td>Interleukin 6</td>
<td>12/41/42</td>
<td>96%</td>
<td>75%</td>
<td>24%</td>
<td>98%</td>
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**Table 4:** Test characteristics for CSF and serum diagnostic markers in different studies.


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count, glucose, and protein concentration in the differentiation of bacterial from aseptic meningitis (sensitivities of 93% [95% CI 89–96] and 97% [95–98], and specificities of 96% [93–98] and 94% [93–96], respectively). In patients who received antibiotic treatment before the lumbar puncture, CSF lactate concentration had a substantially lower sensitivity of 49% (23–75) compared with those not receiving antibiotic pretreatment (98%, 96–100). CSF lactate concentration is less accurate in patients with several other CNS diseases, such as stroke and head trauma, in which the concentrations are raised. Therefore, the usefulness of CSF lactate concentrations in patients pretreated with antibiotics, or those with some other CNS diseases, is probably limited.67,68

CSF concentrations of cortisol, heparin-binding protein, soluble triggering receptor expressed on myeloid cells 1, interleukin 6, interleukin 12, interleukin 1β, tumour necrosis factor α, complement component B, and complement component 3 have been studied as markers for acute bacterial meningitis in single studies of children or adults (table 4).65–70 Most of these studies included fewer than 40 patients, limiting the generalisability of the results. The concentration of CSF complement component B had 100% sensitivity and specificity in adults, and the performance of complement component 3 and heparin-binding protein was excellent (complement component 3 sensitivity 100%, specificity 95%; heparin-binding protein sensitivity 100%, specificity 99.2%) in the differentiation of bacterial from aseptic meningitis.65,66

Retrospective studies have shown that serum concentrations of C-reactive protein and procalcitonin are highly discriminatory between paediatric bacterial and viral meningitis.71,72 A study of 507 children showed a specificity of C-reactive protein of 100% (95% CI 97–100) for patients with a C-reactive protein concentration greater than 40 mg/L, and a sensitivity of 93% (90–96) for identification of acute bacterial meningitis cases.71 A meta-analysis of six retrospective studies in 198 children showed that increased serum procalcitonin (≥0.5 μg/L) and C-reactive protein (≥20 mg/L) concentrations were associated with acute bacterial meningitis, with an odds ratio of 434 (95% CI 57·0 to >1000·0) for increased procalcitonin, and 9·9 (4·8–20·8) for increased C-reactive protein concentrations.72 However, whether these additional CSF and serum tests add any value to standard tests is unclear.

Additional diagnostic dilemmas

In resource-poor settings, the differentiation between acute bacterial meningitis, cryptococcal meningitis, tuberculous meningitis, and cerebral malaria can be very difficult when patients have received prehospital antibiotic treatment.69,73 Abnormalities in the CSF white blood cell count and CSF protein and glucose concentrations are usually less pronounced in patients with acute bacterial meningitis who are receiving antibiotics than in those who are not, and could therefore resemble CSF abnormalities that are typical for patients with tuberculous meningitis. Molecular diagnostic methods (e.g., PCR) can help to identify the causative microorganism in these patients,69 but are often not available in resource-poor settings and, if available, are not helpful if the result is negative. In these patients, treatment for both bacterial and tuberculous meningitis is usually started, and repeated lumbar puncture is done to assess the treatment effect.

Antibiotics kill susceptible bacteria in the CSF rapidly, rendering the sample sterile within about 8 h of administration.74 In a retrospective case series of 92 patients with suspected acute bacterial meningitis, CSF culture was positive in 73% of patients who had a lumbar puncture up to 4 h after start of antibiotic treatment, compared with 11% of patients who had a later lumbar puncture.76 Antibiotic treatment also causes the CSF white blood cell count to decrease in the subsequent 48–72 h, with a rise in the proportion of mononuclear cells, and an increase in CSF glucose, which is usually very low in untreated acute bacterial meningitis, to normal concentrations.77

When the suspicion of acute bacterial meningitis in a patient is sufficiently high to start empirical antibiotic treatment, but the diagnosis has not been confirmed directly by characteristic CSF findings or Gram stain, the diagnosis needs to be reassessed after admission. Results of blood and CSF cultures, cryptococcal antigen testing, Ziehl–Neelsen or India ink stains, and, when available, PCR results of CSF, will subsequently become available in the days after admission. If these tests remain negative or are unavailable, and the patient has no response to the initiated therapy, diagnostic uncertainty continues, particularly in patients in resource-poor settings. In these patients, cryptococcal, tuberculous, and partly treated acute bacterial meningitis are difficult to distinguish apart, and physicians often start empirical treatments for tuberculous and acute bacterial meningitis simultaneously.78 A repeated lumbar puncture could be necessary to repeat microbiological tests on CSF and to assess the response to therapy. A rapid decrease in CSF cell count and protein, and an increase in glucose, is expected in patients with acute bacterial meningitis but not in those with tuberculous meningitis.79

Conclusions and future directions

Early recognition of acute community-acquired bacterial meningitis is essential to improve the prognosis of the disease. Clinical assessment alone is insufficient to exclude acute bacterial meningitis, and a lumbar puncture with CSF analysis is needed in all patients with suspected acute bacterial meningitis. In some cases, cranial imaging is needed before lumbar puncture to detect brain shift; in these patients, empirical antibiotic treatment should be given before imaging. Molecular diagnostic methods have emerged in the diagnostic process for acute bacterial meningitis, although costs...
restrict their use worldwide. Well designed studies of diagnostic accuracy are needed for new CSF variables that add potential value to standard laboratory tests. Prediction models can be used to estimate the risk of acute bacterial meningitis, but these models need to be refined and validated further in several settings and populations. Clinical judgment of individual patients by their physicians remains the most important factor in the diagnosis of acute bacterial meningitis.

Contributors
All authors contributed to writing and editing of the review, and all authors approved the final version.

Conflicts of interest
We declare that we have no conflicts of interest.

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