

# The diagnosis and management of acute bacterial meningitis in resource-poor settings

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Acute bacterial meningitis is more common in resource-poor than resource-rich settings. Survival is dependent on rapid diagnosis and early treatment, both of which are difficult to achieve when laboratory support and antibiotics are scarce. Diagnostic algorithms that use basic clinic and laboratory features to distinguish bacterial meningitis from other diseases can be useful. Analysis of the CSF is essential, and simple techniques can enhance the yield of diagnostic microbiology. Penicillin-resistant and chloramphenicol-resistant bacteria are a considerable threat in resource-poor settings that go undetected if CSF and blood can not be cultured. Generic formulations of ceftriaxone are becoming more affordable and available, and are effective against meningitis caused by penicillin-resistant or chloramphenicol-resistant bacteria. However, infection with *Streptococcus pneumoniae* with reduced susceptibility to ceftriaxone is reported increasingly, and alternatives are either too expensive (eg, vancomycin) or can not be widely recommended (eg, rifampicin, which is the key drug to treat tuberculosis) in resource-poor settings. Additionally, improved access to affordable antibiotics will not overcome the problems of poor access to hospitals and the fatal consequences of delayed treatment. The future rests with the provision of effective conjugate vaccines against *S pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis* to children in the poorest regions of the world.

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## Introduction

Acute bacterial meningitis is at least ten times more common in developing countries than in the rest of the world<sup>1</sup> and is almost always fatal without treatment.<sup>2</sup> Survival depends on accurate diagnosis and the early administration of antibiotics,<sup>3</sup> neither of which is easy to achieve when resources are limited. Additional factors, such as advanced HIV infection, malnutrition, and antibiotic-resistant bacteria, complicate the management of the infected patient. For these reasons, acute bacterial meningitis presents an exceptional challenge to physicians working in resource-poor settings. We have focused this review on the common clinical problems that arise when a patient with acute bacterial meningitis presents to a doctor and we review the evidence available to resolve these problems in settings with limited resources.

## Diagnosis of acute bacterial meningitis

### Clinical features

The clinical features of acute bacterial meningitis usually develop over 24–48 hours but their nature varies according to the age of the patient. Panel 1 outlines the common symptoms and signs of bacterial meningitis in older children and adults. The triad of headache, neck stiffness, and photophobia is difficult to assess in young children and other features should be sought. Irritability, reduced conscious level, a bulging fontanel, poor feeding, cyanosis, “staring eyes”, and seizures outside the age range for febrile convulsions have all been independently associated with bacterial meningitis in young children.<sup>4–6</sup>

Neck stiffness, fever, and altered mental state are among the most commonly reported signs and symptoms in adults with bacterial meningitis,<sup>7</sup> although one or more of these signs and symptoms is commonly absent.<sup>8,9</sup> The authors of a recent series reported that all three features were present in only 44% of 696 adults with

proven bacterial meningitis,<sup>10</sup> but the absence of all three excluded the diagnosis, with a sensitivity of 99%.<sup>10,11</sup>

Neck stiffness is commonly regarded as the most specific sign of bacterial meningitis but it is reported by only 50–90% of patients<sup>4,7</sup> and is frequently absent in patients who are comatose. Conversely, neck stiffness can also be a sign of subarachnoid haemorrhage, tetanus,<sup>12</sup> or other infections that are associated with a high fever. Neck stiffness has been reported by 13% of adult general medical inpatients (35% of elderly patients) who did not have meningitis,<sup>13</sup> and in a Kenyan paediatric study only 40% (30 of 76) of children with neck stiffness had a final diagnosis of bacterial meningitis.<sup>14</sup> The poor diagnostic value of neck stiffness is not improved by Kernig’s or Brudzinski’s signs because neither has a sensitivity of more than 10%.<sup>8</sup>

### Panel 1: Common symptoms and signs of bacterial meningitis and their frequency in older children and adults

#### Symptoms

Fever (75–95%)  
Headache (80–95%)  
Photophobia (30–50%)  
Vomiting (90% of children; 10% of adults)

#### Signs

Neck stiffness (50–90%)  
Confusion (75–85%)  
Kernig’s sign\* (5%)  
Brudzinski’s signs† (5%)  
Focal neurological deficit (20–30%)  
Fits (15–30%)  
Rash (10–15%)

\*Resistance to passive extension of the knee when the hip is flexed at 90°.

†Spontaneous flexion of the hips and knees on passive flexion of the neck.



**Figure 1: A low-resource setting and the clinical features of bacterial meningitis**

(A) A general medical ward in Malawi: a typical setting in the developing world for the management of bacterial meningitis. (B) Meningitis-associated subconjunctival haemorrhage. (C) Fine petechial rash associated with disseminated infection and meningitis due to *Staphylococcus aureus*. (D) Ecchymosis associated with *Streptococcus suis* bacteraemia and meningitis. (E) The petechial skin rash that accompanies meningitis due to *Neisseria meningococcus*. (F) *Streptococcus pneumoniae* bacterial meningitis with right third-cranial-nerve palsy and severe oral herpes simplex infection, which are commonly associated with pneumococcal meningitis.

Focal neurological deficit or a history of seizures is present in 15–30% of adults and children<sup>7,10,11,15,16</sup> but also occurs in patients with tuberculous or cryptococcal meningitis. A petechial or purpuric skin rash is seen in about 10–15% of adults with bacterial meningitis.<sup>7,10</sup> Most rashes are associated with meningococcal disease, although they can also be seen in patients with pneumococcal, staphylococcal, or haemophilus bacteraemia (figure 1). An inflammatory arthritis can occur in a few patients, particularly those with meningococcal disease.<sup>17</sup>

#### Causative organisms and differential diagnoses

*Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis* are the most important causes of

acute bacterial meningitis worldwide. However, several other infections can cause acute meningitis with similar clinical features (panel 2). Some of these infections are associated with specific population groups; for example, *Streptococcus suis* is the commonest cause of acute bacterial meningitis in southeast Asia<sup>18</sup> but occurs rarely elsewhere. HIV infection is an important factor that affects the aetiology of acute meningitis. *S pneumoniae* is the commonest cause of acute bacterial meningitis in HIV-infected patients, but meningitis caused by *Mycobacterium tuberculosis* and *Cryptococcus neoformans* is also common in this group, and can be difficult to distinguish from acute bacterial meningitis on clinical grounds alone.<sup>19,20</sup> Meningitis caused by these two organisms often presents with symptoms that occur over

days or weeks,<sup>21</sup> but both organisms can cause fulminant disease with marked neck stiffness and rapid progression to coma.<sup>20,22</sup>

Partially treated acute bacterial meningitis is a common and difficult diagnostic dilemma in resource-poor settings. In some countries, antibiotics can be bought freely over the counter; for example, the authors of a Vietnamese study reported 61% of 435 adults with acute bacterial meningitis had undefined antibiotic treatment in the community before admission to hospital.<sup>23</sup> The differentiation of partially treated acute bacterial meningitis from tuberculous meningitis and the other causes of aseptic meningitis is extremely difficult with only limited diagnostic facilities. In high-income countries, most cases of aseptic meningitis are caused by viruses, particularly enteroviruses.<sup>24</sup> A viral aetiology is difficult to confirm in resource-poor settings but might account for 14–25% of all meningitis illnesses in African regions that have a high HIV seroprevalence;<sup>25,26</sup> most of these cases are likely to be due to enteroviruses.<sup>27</sup>

The distinction of cerebral malaria from acute bacterial meningitis can be difficult, particularly in children from sub-Saharan Africa where malaria is often over-diagnosed.<sup>28</sup> Both diseases are common causes of headache, fever, and altered consciousness; the authors of a trial in Malawi reported that 42% of 426 adult patients who were diagnosed with bacterial meningitis received antimalarial treatment during the course of their illness but only two patients had a final diagnosis of malaria.<sup>29</sup> Investigators in Kenya found that 14% of comatose children under 1 year who had malaria parasites seen on a blood film had proven bacterial meningitis; the investigators concluded that acute bacterial meningitis must be actively excluded in all comatose children in sub-Saharan Africa, regardless of whether malarial parasites are seen in the blood.<sup>30</sup>

## Investigations

### Blood tests

The microscopic search for malarial parasites is an important blood test in regions where malaria is endemic. The test has a negative predictive value greater than 95%,<sup>31</sup> although this is commonly not appreciated.<sup>32</sup> A negative blood film from a febrile patient should prompt a thorough search for an alternative diagnosis. In seriously ill children from regions where malaria is endemic, a blood film that is positive for malaria is hard to interpret, and analysis of the CSF is often needed to determine whether or not the patient has acute bacterial meningitis.<sup>33,34</sup>

Full blood count and electrolyte concentrations, even when available, are of limited value in the diagnosis of acute bacterial meningitis. The total white cell count in the peripheral circulation is usually raised due to a neutrophilia but can be lowered in severe infection. Blood glucose concentration should be measured, where possible, because it contributes to the interpretation of the results of the CSF analysis.

### Panel 2: Common infectious causes of meningitis in resource-poor settings

#### Bacterial

- *Streptococcus pneumoniae* (commonest cause worldwide; associated with HIV infection)
- *Haemophilus influenzae* type B
- *Neisseria meningitidis* (serogroups A, W-135, C, and X cause epidemics in Africa; serogroups B and C are more common in Europe, North America, Australia, and east Asia)
- *Streptococcus suis* (commonest cause of bacterial meningitis in southeast Asia)
- *Staphylococcus aureus* (uncommon)
- Group B streptococci (common cause in neonates)
- *Listeria monocytogenes* (neonates, elderly people, and immune compromised)
- *Enterobacteriaceae* spp (neonates, elderly people, and immune compromised)
- Non-typhi *Salmonella* sp (patients in Africa who are infected with HIV)
- *Mycobacterium tuberculosis* (more common with HIV infection)
- *Treponema pallidum*

#### Fungal

- *Cryptococcus neoformans* (advanced HIV infection)

#### Parasitic

- *Angiostrongylus cantonensis* and *Gnathostoma spinigerum* (eosinophilic meningitis in southeast Asia)
- *Toxocara canis* (worldwide)

#### Viral

- Herpes viruses (herpes simplex and varicella zoster)
- Enteroviruses

Blood cultures are positive in about two-thirds of adult patients with bacterial meningitis in Europe<sup>30</sup> and about a third in poorer countries.<sup>23,29</sup> Test results take at least 24 hours to become available and, therefore, cannot contribute to the initial management strategy. However, test results can be useful, particularly when CSF was not obtained before antibiotics were given and when empirical therapy fails. In many countries, the facilities for blood culture are unavailable.

A rapid HIV test is an important investigation in areas of high HIV prevalence<sup>35</sup> because a positive test result broadens the differential diagnosis: cryptococcal meningitis, tuberculous meningitis, and toxoplasma meningoencephalitis should be considered.

### Lumbar puncture

Analysis of the CSF is most likely to establish or exclude a diagnosis of meningitis and determine its cause; however, such tests are not often done. A survey of inpatient paediatric practice in 14 Kenyan hospitals found that 7% of 639 children who were admitted had fever and a stiff neck; 13 were diagnosed with acute bacterial meningitis but none had a lumbar puncture.<sup>36</sup>

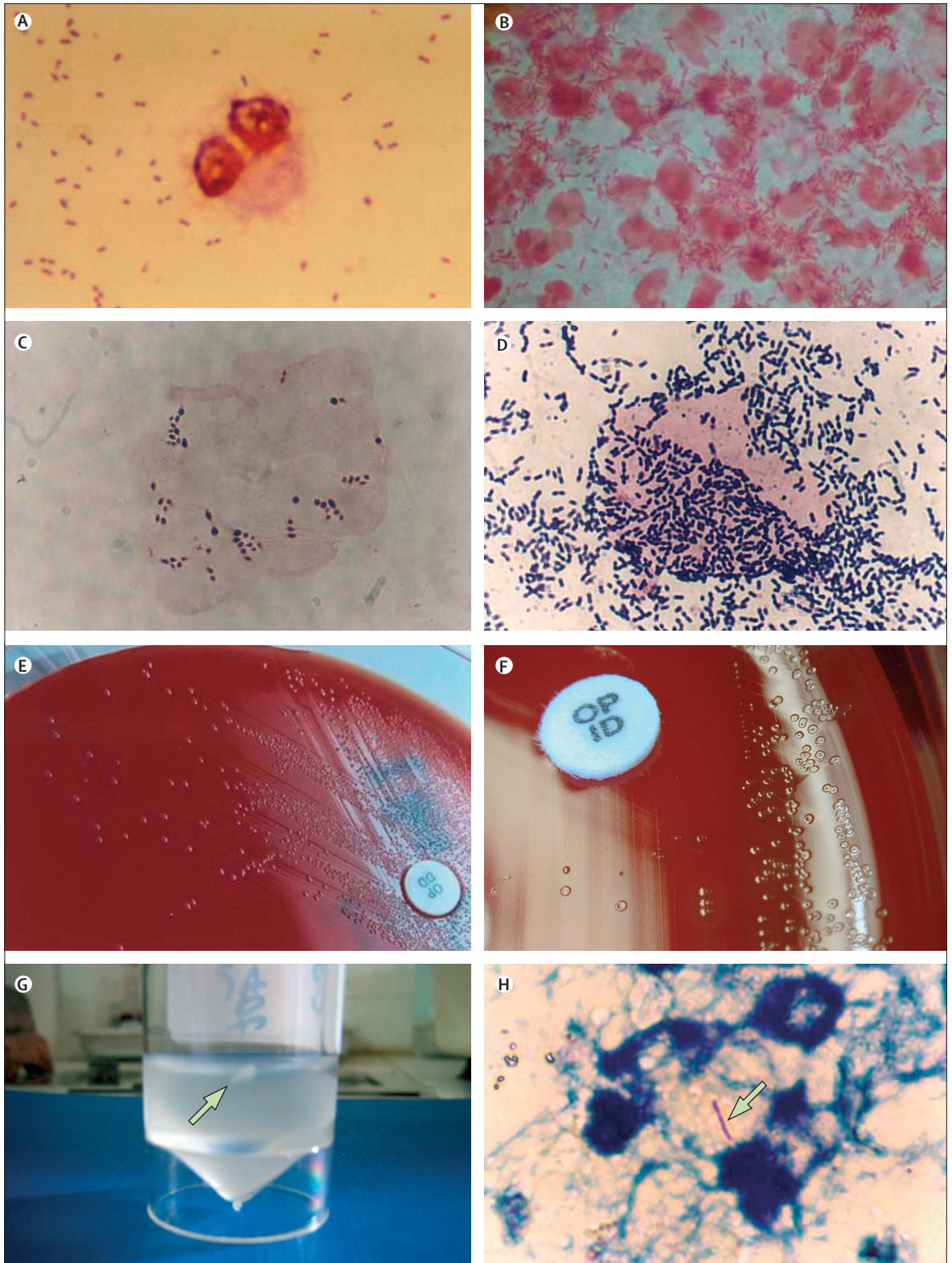
Lumbar puncture is often delayed or deferred owing to concern about the risk of cerebral herniation.<sup>37</sup> We believe that this risk is overemphasised and needs to be assessed in the context of the care available. In high-income countries, the usual practice is to obtain brain imaging before lumbar puncture in patients with focal neurological

signs (including new-onset seizure activity), papilloedema, reduced level of consciousness, or in the immuno-

compromised.<sup>38-40</sup> The imaging approach is inappropriate for many practitioners in resource-poor settings; even

**Figure 2: The microbiological features of bacterial meningitis**

(A) Gram-positive diplococci of *Streptococcus pneumoniae* in the CSF. (B) Neutrophils and Gram-negative rods in the CSF of an elderly patient with meningitis due to *Escherichia coli*. (C) Gram stain of CSF showing intracellular Gram-positive cocci of *Streptococcus suis*; Gram staining alone can not differentiate between *S suis* and *S pneumoniae*. (D) Gram stain of a skin smear taken from a petechial lesion that contains many Gram-positive *S pneumoniae* diplococci. (E) Optochin-disc test to differentiate *S pneumoniae* from other streptococcal species: *S pneumoniae* is almost always susceptible, whereas all other streptococci are resistant and will grow up to the disc margin. (F) Optochin-sensitive *S pneumoniae* cultured from the CSF (bacteria do not grow to the disc margin). (G) Cloudy CSF from an adult with bacterial meningitis. A fibrous spider clot (arrow) formed after 1 hour. Spider clots are not diagnostic for tuberculous meningitis but can form when the concentration of protein in the CSF is high (>1.5 g/dL), regardless of aetiology. (H) Single acid-fast bacilli (arrow) in the CSF of an adult with tuberculous meningitis (Ziehl-Neelsen stain; counter stain methylene blue).



when imaging is available, cerebral herniation cannot reliably be predicted by abnormalities on brain CT and a normal CT does not exclude the risk of coning.<sup>41</sup> In our opinion, the omission of a lumbar puncture for fear of complications carries a greater risk of death in a resource-poor setting due to inaccurate diagnosis than the inherent risks that are associated with the procedure, regardless of focal signs or a reduced level of consciousness.

### Analysis of the CSF

Measurement of CSF opening pressure is of limited diagnostic value because it can be raised in patients with meningitis of any aetiology, and up to 10% of patients with acute bacterial meningitis can have normal CSF opening pressure at presentation.<sup>7</sup>

When laboratory facilities are limited, the gross appearance of the CSF is often used to determine the likelihood of acute bacterial meningitis. Turbid CSF implies the presence of inflammatory cells, but can also indicate red cells or microorganisms. In Kenyan children, turbid CSF predicted probable or proven bacterial meningitis in less than 40% of cases and was seen in at least 1% of patients who did not have bacterial meningitis. Clinicians who made a diagnosis of acute bacterial meningitis on the basis of neck stiffness or CSF turbidity were likely to miss 30% (21 of 71) of proven or probable cases.<sup>4</sup> In Vietnamese adults, 2% of patients with bacterial meningitis and 57% of patients with tuberculous meningitis had clear CSF at presentation.<sup>42</sup>

Microscopic assessment of the number and type of cells in the CSF provides important diagnostic information. The total CSF white cell count exceeds 1000 cells per  $\mu\text{L}$  in more than 90% of adult patients in Europe with acute bacterial meningitis but has wide variation; considerably lower cell counts are seen in children<sup>14</sup> and in immunocompromised patients,<sup>43</sup> and acellular CSF has been reported in immunocompetent patients with meningococcal<sup>44,45</sup> and pneumococcal meningitis.<sup>46</sup> Neutrophils are usually the predominant cell type in the CSF of patients with bacterial meningitis, but high numbers of neutrophils can also be seen early in the course of viral and tuberculous meningitis.<sup>20,47</sup>

Biochemical analysis of the CSF can help to distinguish bacterial meningitis from other infectious and inflammatory processes but can be difficult when laboratory facilities are scarce. Raised CSF protein concentration is a non-specific indicator of acute bacterial meningitis and many other inflammatory disorders. Low CSF glucose concentration ( $<2.5$  mmol per L or  $<50\%$  plasma value) is a more useful finding because it is seen in more than 90% of patients with acute bacterial and tuberculous meningitis but not in most cases of viral meningitis.<sup>48</sup> In general, viral<sup>49</sup> and cryptococcal meningitis<sup>50</sup> cause less pronounced biochemical changes compared with bacterial or tuberculous meningitis.

### Panel 3: Ways to improve the diagnostic yield of microbiology

- Examine CSF before or shortly after antibiotics are started
- Submit a large volume of CSF ( $>5$  mL) for microbiological analysis
- Centrifuge at high relative centrifugal force (3000 g) for 20 min, particularly if the diagnosis of tuberculous meningitis is considered, and stain and culture the deposit (biochemical tests can be done on the supernatant)
- Examine the microscope slide carefully for at least 10 min. If searching for acid-fast bacilli, increase to at least 20 min and first search the areas with most cells

When microscopic and biochemical analyses are not available, the semiquantitative estimation of glucose, protein, and leukocyte esterase concentrations in the CSF with urine dipsticks might be considered. The results of a study in Kuwait of 234 CSF samples implied that urine dipsticks accurately identified all patients with healthy CSF and 97% of patients with abnormal CSF.<sup>51</sup> In addition, the dipsticks could distinguish viral from bacterial meningitis in 98% of cases. The authors of several subsequent studies have reported similar results,<sup>52-54</sup> although the sensitivity can be considerably lower in clear CSF compared with turbid CSF.<sup>55</sup> Additional tests for nitrites in CSF can improve the sensitivity.<sup>56</sup> The usefulness of dipsticks to distinguish bacterial from cryptococcal or tuberculous meningitis is uncertain.

### Diagnostic microbiology

Gram staining of the CSF for meningitis-causing bacteria is 50–90% sensitive<sup>57</sup> and is positive in up to 15% of cases that are negative after subsequent culture of the CSF.<sup>7</sup> The specificity of Gram staining the CSF to diagnose bacterial meningitis is nearly 100%<sup>57</sup> (figure 2) and is useful to direct initial therapy, particularly when culture facilities are unavailable. With good bedside and laboratory practice, the Ziehl-Neelsen and India ink stains can be positive in 50–80% of cases of tuberculous and cryptococcal meningitis (panel 3).<sup>58-60</sup>

CSF culture is the gold standard for the diagnosis of bacterial meningitis and enables the determination of antibiotic sensitivities to direct appropriate therapy. Pre-presentation antibiotic exposure is common in resource-poor settings<sup>23,29</sup> and reduces the sensitivity of CSF culture and alters the CSF parameters: cell counts are reduced, lymphocytes can predominate, and glucose concentration rises.<sup>61-63</sup> In a study of 128 children with bacterial meningitis, 97% who had not taken antibiotics before lumbar puncture were culture positive; this figure fell to 67% and 56% for patients who had received oral or parenteral antibiotics, respectively.<sup>61</sup>

The diagnostic usefulness of bacterial-antigen detection in the CSF by card immunochromatography or by latex agglutination is controversial. Some authors have reported high specificity for the diagnosis of pneumococcal, meningococcal, and haemophilus meningitis<sup>64-66</sup> and increased sensitivity compared with culture in antibiotic-exposed patients.<sup>67,68</sup> Other investigators have

	Age group	Requirements	Aim	Sensitivity (%)	Specificity (%)
Chavenet and co-workers <sup>77</sup>	Adults and children	Microscopy and biochemistry	ABM vs viral	100%	71% 85%
Nigrovic and co-workers <sup>75</sup>	Children	History, microscopy, and biochemistry	ABM vs viral	100%	66%
Hoen and co-workers <sup>78</sup>	Adults and children	Microscopy and biochemistry	ABM vs viral	89% 100%	94% 70%
*†Berkley and co-workers <sup>4</sup>	Children	History and examination	ABM	79%	80%
†Thwaites and co-workers <sup>42</sup>	Adults	History, microscopy, and full blood count	TBM vs ABM	86%	79%

Only two studies were developed in resource-poor countries, and all except one (\*) relied on laboratory data.

†Developed in resource-poor countries. ABM=acute bacterial meningitis. TBM=tuberculous meningitis.

**Table 1: Comparison of five indicator or prediction rules for the early determination of the aetiology of meningitis**

	Intended population	Predictive clinical parameters (and score if applicable)	Suggested diagnostic rule
Thwaites and co-workers <sup>42</sup>	Adults (>14 years)	Age $\geq 36$ years=score 2 or age <36 years=score 0; White blood cell count $\geq 15\,000 \times 10^3$ per mL=score 4 or white blood cell count <15 000 $\times 10^3$ per mL=score 0; History of illness $\geq 6$ days=score -5 or 6 days=score 0; CSF total white cell count $\geq 750 \times 10^3$ per mL=score 3 or CSF total white cell count <750 $\times 10^3$ per mL=score 0; CSF neutrophils $\geq 90\%$ =score 4 or <90%=score 0	A total score >4 points is suggestive of bacterial meningitis; a total score $\leq 4$ points is suggestive of tuberculous meningitis
Berkley and co-workers <sup>4</sup>	Children ( $\geq 60$ days)	Bulging fontanel Neck stiffness Cyanosis Impaired consciousness Partial seizures Seizures beyond the age of febrile convulsions	Bacterial meningitis is probable if one or more of these findings is present, and a lumbar puncture should be done

**Table 2: Predictors of acute bacterial meningitis in resource-poor settings**

found these tests contribute little to the diagnosis of bacterial meningitis and are not sensitive enough, particularly in pretreated individuals.<sup>69-71</sup> The performance of the cryptococcal-antigen latex agglutination test is more reliable, with 93–100% sensitivity and up to 98% specificity.<sup>72</sup> However, these tests are expensive and are best reserved for patients in whom an initial microscopic analysis does not contribute to the diagnosis or when the facilities for microscopy and culture are unavailable.<sup>69</sup> No equivalent rapid tests are available for the diagnosis of tuberculous meningitis.

### Diagnostic prediction rules and algorithms

Many hospitals in low-income countries do not have culture facilities. Clinicians, therefore, rely heavily on clinical features and simple laboratory data to make a diagnosis. Several diagnostic rules have been proposed that use the clinical features at presentation to predict the diagnosis of bacterial meningitis<sup>4,73,74</sup> or to distinguish pyogenic from other types of meningitis (table 1).<sup>42,75,76,77,78</sup> However, only two such rules have been developed for resource-poor settings (table 2).

There are important limitations to these rules. First, CSF culture is the gold standard against which prediction rules are measured but culture is not sensitive enough

itself, particularly where prehospital antibiotic exposure is common. Indeed, some of the diagnostic rules that were developed in wealthy countries excluded pretreated patients whose cultures were negative,<sup>76,77</sup> which prevents the use of these rules in many resource-poor settings. Second, changes in the CSF white cell count, and protein and glucose concentrations depend on age, race, and organism<sup>73,77</sup> and can not necessarily be generalised among different populations. Most rules aim to distinguish between bacterial meningitis, viral meningitis, or uninfected CSF; few rules aim to differentiate bacterial from tuberculous<sup>42</sup> or cryptococcal meningitis, both of which are major causes of meningitis in low-income countries. Third, some rules rely on the results of microscopic and biochemical tests, which might be unavailable in many hospitals in low-income countries. Finally, the performance of the diagnostic rules in settings with high HIV seroprevalence is likely to be substantially altered. Ugandan investigators developed a diagnostic algorithm for the management of adults with CNS infection; they suggested that a rapid HIV test and lumbar puncture were the crucial initial investigations followed by tests for cryptococcus in the CSF if the HIV test was positive.<sup>35</sup> Further assessments of this potentially useful algorithm have not been published.

### Treatment of bacterial meningitis

#### Choice of antibiotic therapy

Ceftriaxone has become affordable to many developing countries since its patent expired in 2005.<sup>79,80</sup> In 2007, WHO guidelines for the treatment of bacterial meningitis in Africa recommended ceftriaxone as first-line therapy.<sup>81</sup> Nevertheless, penicillin (ampicillin/amoxicillin or benzylpenicillin) and chloramphenicol are still used in many developing countries. The authors of a recent systematic review and meta-analysis compared the efficacy of third-generation cephalosporins with conventional antibiotics (mostly ampicillin and chloramphenicol) and concluded that there was no significant difference in outcome with respect to death or neurological sequelae.<sup>82</sup> However, much of the data came from studies done in the 1980s when the incidence of penicillin or chloramphenicol resistance was low. The authors of more recent studies suggest that resistance to penicillin or chloramphenicol in isolates of *S pneumoniae* or *H influenzae* is greater than 20% and that more than 10% of isolates are resistant to both drugs.<sup>83-86</sup>

The rising incidence of meningitis due to drug-resistant organisms is a major threat and poses particular problems in resource-poor settings. Resistance can go unnoticed owing to the lack of facilities for culture and susceptibility testing, and second-line antibiotics might be unobtainable. Ceftriaxone-resistant *S pneumoniae* is now a major global concern; in Africa, about 5% of *S pneumoniae* isolates have reduced susceptibility to ceftriaxone.<sup>81</sup> Reports of ceftriaxone-resistant *H influenzae* and *N meningitidis* are

still rare, although the WHO highlights the importance of improvements in the capacity of regional and national laboratories to document drug resistance and the implementation of longitudinal surveillance programmes to detect changes in resistance patterns.<sup>81</sup>

What are the options to treat patients in resource-poor settings who have meningitis due to *S pneumoniae* that has reduced susceptibility to ceftriaxone? In developed countries, vancomycin is recommended in combination with ceftriaxone,<sup>87</sup> but vancomycin is expensive and rarely available in resource-poor settings. The fluoroquinolones might be effective but there are few clinical data to confirm their efficacy. Rifampicin is cheap, widely available, achieves adequate concentrations in the CSF, and is active against ceftriaxone-resistant *S pneumoniae*.<sup>88,89</sup> However, the use of rifampicin for non-tuberculous infection would risk an increase in the incidence of rifampicin-resistant tuberculosis and, therefore, can not be recommended for the widespread empirical treatment of resistant pneumococcal disease.

#### Route of administration and duration of therapy

The route and duration of therapy are important considerations in resource-poor settings because the skills and equipment needed for intravenous treatment are often scarce. Ceftriaxone has the advantage of being effective as a once-a-day dose and can be given intravenously or intramuscularly (table 3).<sup>90,91</sup>

Uncomplicated meningococcal disease can be treated effectively with one intramuscular dose of ceftriaxone or oily chloramphenicol<sup>80</sup> and both are recommended by the WHO to treat epidemics of meningococcal meningitis in Africa.<sup>81</sup> Therapy should be extended to at least 5 days in non-epidemic situations in patients who are younger than 24 months old or if fever, coma, or convulsions last for more than 24 hours.<sup>81</sup>

The optimum duration of therapy for meningitis caused by other bacteria is uncertain. A randomised trial in Chilean children who were older than 3 months compared 7 days' treatment with ceftriaxone with 4 days' treatment in patients who made a good initial recovery; the authors reported similar outcomes in the two groups.<sup>92</sup> Most cases in this trial were caused by *N meningitidis* or *H influenzae*. The investigators in a trial in India compared 7 days' therapy with 10 days' therapy for childhood meningitis caused mostly by *S pneumoniae* and reported similar outcomes between the groups.<sup>93</sup> The WHO recommends that 5 days of antibiotic therapy is sufficient for most immunocompetent patients who make a prompt and uncomplicated recovery. Therapy should be extended in patients with persistent fever, seizures, coma, and in patients who are immunocompromised. Many authorities in high-income countries are more conservative and recommend at least 7 days' treatment for haemophilus and meningococcal meningitis and 10–14 days' treatment for pneumococcal meningitis.<sup>91</sup> The evidence that supports these recommendations is scant and further randomised trials are required.

More than 33 million adults and children live with HIV worldwide: 90% of those affected live in low-income countries.<sup>94</sup> In such settings, the outcome from bacterial meningitis is worse in patients who are co-infected with HIV.<sup>95,96</sup> Furthermore, for reasons unknown, antibiotic resistance is more common in patients who are infected with HIV.<sup>97</sup> There are no controlled trials of the optimum duration of therapy in patients with HIV, but owing to the poor treatment outcomes many authorities recommend a minimum of 10 days' treatment for meningitis caused by *S pneumoniae* and *H influenzae*, and 7 days' treatment for meningitis caused by *N meningitidis*. Non-typhoidal salmonella meningitis is an important

	Dose in children (≤14 years)	Dose in adults (>14 years)	Route	Duration of therapy	Comments
Ceftriaxone	100 mg/kg/day (single dose)	2 g/day (single dose)	Intramuscular or intravenous	Age <2 months ≥7 days Age >2 months ≥5 days*†	The antibiotic of choice if available and affordable
Cefotaxime	225–300 mg/kg/day (3–4 divided doses)‡	8–12 g/day (4–6 divided doses)	Intramuscular or intravenous	Age <2 months ≥7 days Age >2 months ≥5 days†	Similar to ceftriaxone but less conveniently given
Benzylpenicillin	0.3 mU/kg/day (4–6 divided doses)§	24 mU/day (6 divided doses)	Intravenous	Age <2 months ≥7 days Age >2 months ≥5 days†	Most <i>Haemophilus influenzae</i> are resistant; <i>Streptococcus pneumoniae</i> resistance is increasing
Ampicillin or amoxicillin	300 mg/kg/day (4 divided doses)¶	12 g/day (6 divided doses)	Intramuscular, intravenous, or oral**	Age <2 months ≥7 days Age >2 months ≥5 days†	Resistance as for benzylpenicillin. Treatment of choice for listeriosis
Chloramphenicol	100 mg/kg/day (4 divided doses)††	100 mg/kg/day (4 divided doses)	Intramuscular, intravenous, or oral	Age <2 months ≥7 days Age >2 months ≥5 days	High proportion of <i>H influenzae</i> and <i>S pneumoniae</i> are resistant

Regimens are based on those recommended by the Infectious Diseases Society of North America<sup>92</sup> and the WHO.<sup>81</sup> \*A single dose of up to 4 g is effective in meningococcal epidemic conditions in Africa. †Extend therapy beyond 5 days if fever, coma, or seizures still present at day 5 of therapy or if the patient is immunocompromised. Suggest minimum of 10 days in patients infected with HIV who have proven or suspected *S pneumoniae* meningitis. ‡Reduce to 150 mg/kg/day (2–3 divided doses) in neonates. §Reduce to 0.2 mU/kg (6–8 divided doses) if younger than 28 days old, and to 0.1 mU/kg (8–12 divided doses) if younger than 7 days. ¶Reduce to 200 mg/kg/day in those younger than 1 month and to 150 mg/kg/day if younger than 7 days. Many clinicians would also add gentamicin (7.5 mg/kg/day in 3 divided doses) when treating neonates. \*\*Less than half of ampicillin dose is absorbed orally; therefore, use amoxicillin. ††A single intramuscular dose (≈3 g) of long-acting oily chloramphenicol is effective in meningococcal epidemic conditions in Africa.

**Table 3: Summary of dose, route, and duration of antibiotics for the treatment of bacterial meningitis in resource-poor settings**

cause of bacterial meningitis in patients in sub-Saharan Africa who are infected with HIV; this meningitis requires at least 3 weeks of therapy.<sup>98</sup>

#### Counterfeit and substandard drugs

Counterfeit drugs are an increasing problem, and anti-infective drugs are the most commonly implicated, in particular penicillin, tetracycline, and chloramphenicol.<sup>99</sup> Reports of counterfeit ceftriaxone are rare, although the drug might be substandard for other reasons. Some generic preparations of ceftriaxone do not meet the manufacturing standards that are set by Roche for the proprietary drug rocephin<sup>100</sup> or have similar efficacy.<sup>101</sup> Additionally, the quality of the drug can be compromised by failure to use the drug within its shelf life (3 years for ceftriaxone) or storage of the drug at high temperatures (>25°C for most antibiotics). The clinical consequences of counterfeit or substandard antibiotics include treatment failure, increased risk of drug resistance, and unpredictable toxicity and side-effects.

### Adjunctive therapy

#### Dexamethasone

Adjunctive corticosteroids have long been suggested for the treatment of bacterial meningitis, although evidence that confirms their beneficial effect has been hard to obtain. The authors of a European trial of 301 adults showed that dexamethasone significantly reduced death and neurological sequelae.<sup>102</sup> Consequently, adjunctive corticosteroid therapy has been widely adopted in many high-income countries.<sup>87</sup> Whether the same recommendations should apply to the developing world is uncertain. The authors of three large randomised trials—two in children<sup>83,103</sup> and one in adults<sup>29</sup>—failed to show any benefit of dexamethasone. Patients in these trials differed substantially from those in the European trial: in all three studies, late presentation and prehospital antibiotic exposure were common. In the trials from Malawi, a quarter of the children (83) and 90% of the adults (29) were infected with HIV compared with none of the patients in the European trial. However, the authors of a recent trial from Vietnam have suggested that dexamethasone reduced the incidences of mortality and disability in adults with microbiologically proven bacterial meningitis.<sup>104</sup> Patients in this subgroup were similar to the adults in the European trial but there were also important differences: nearly two-thirds of the Vietnamese adults had antibiotics before recruitment, and *S suis* was the pathogen that was isolated most commonly. Dexamethasone did not reduce fatality or disability in all recruited patients, probably because of the inclusion of some patients with tuberculous meningitis.<sup>104</sup>

Owing to these conflicting data, recommendations for adjunctive steroid therapy in resource-poor settings are difficult. Adults who are HIV negative but who have microbiologically proven disease should probably receive adjunctive dexamethasone but there is little evidence to support the routine use of dexamethasone for other

subgroups. However, physicians should be reassured that there is little evidence that adjunctive corticosteroids cause harm.

#### Glycerol

Glycerol is a hyperosmotic compound that is used in neurosurgery and ophthalmology to reduce intracerebral and intraocular tissue pressure.<sup>105</sup> Glycerol is cheap, widely available, and can be given orally. The authors of a Finnish study that was done 20 years ago first suggested that glycerol might improve outcome from bacterial meningitis.<sup>106</sup> More recently, a trial of dexamethasone, glycerol, or glycerol and dexamethasone in 654 children with bacterial meningitis in Latin America showed a lower incidence of severe neurological sequelae in those treated with glycerol or glycerol and dexamethasone compared with placebo (intravenous saline or oral carboxymethylcellulose).<sup>103</sup> No statistically significant effect on death or deafness was seen in the treatment groups. The results of further controlled trials are awaited before glycerol can be widely recommended for the treatment of bacterial meningitis.

### Other supportive therapies

#### Fluid resuscitation

A patient with acute bacterial meningitis must first be examined for signs of hypovolaemia and for compensated or decompensated shock, which needs urgent treatment. Treatment guidelines are best developed for meningococcal disease,<sup>107</sup> but septic shock is also common in pneumococcal and other meningitides, particularly when they present late.

Half of all children and a third of all adults that present with bacterial meningitis are hyponatraemic.<sup>108,109</sup> Until recently, the syndrome of inappropriate antidiuretic hormone was thought to be the most common cause, and fluid restriction was advocated.<sup>110</sup> This view has been challenged by the authors of a recent meta-analysis of three randomised trials who concluded that intravenous fluid resuscitation was preferable to fluid restriction.<sup>111</sup>

The route of administration and the type of fluid are important considerations in resource-poor settings. A nasogastric tube can be used if consciousness is reduced, although this risks pulmonary aspiration. Resuscitation with intravenous fluids might be quicker and more convenient than with a nasogastric tube but is more expensive, requires supervision by skilled nursing staff, and the risks of accidental overhydration are high. A randomised trial in Papua New Guinea<sup>112</sup> compared milk-based fluid resuscitation by nasogastric tube with intravenous fluid (0.45% Na Cl, 5% dextrose) rehydration in 357 children with bacterial meningitis. Fatality rates were high (17%) but were not significantly altered by treatment allocation. However, the children who were given intravenous fluids had significantly fewer seizures after 72 hours, reduced spasticity at 14 days, and reduced neurological sequelae at 4 weeks after the start of treatment



than the children who had nasogastric resuscitation. In settings where presentation is late, these findings support the use of isotonic intravenous fluid resuscitation to achieve euvoalaemia.

### Prevention

Bacterial meningitis can be prevented by vaccination and by antibiotic chemoprophylaxis.<sup>113</sup> The latter is reserved for localised outbreaks caused by *N meningitidis* and the aim is to eradicate nasopharyngeal colonisation and transmission. Ceftriaxone, rifampicin, and ciprofloxacin are the most effective antibiotics,<sup>113</sup> although rifampicin resistance can develop quickly, and cases of fluoroquinolone-resistant *N meningitidis* have been reported.<sup>114,115</sup> Chemoprophylaxis is rarely used in resource-poor settings because of its cost and the limitations in the public health infrastructure.

In high-income countries, conjugate vaccines to *H influenzae* type-B, *N meningitidis* serogroup C, and *S pneumoniae* led to a striking reduction in invasive disease.<sup>116</sup> In children younger than 5 years, *H influenzae* type-B conjugate vaccine reduced the incidence of haemophilus meningitis by 89% when it was introduced in Kenya in 2001<sup>117</sup> and has virtually eliminated the disease from Uganda after its introduction in 2002.<sup>118</sup> The efficacy of conjugate pneumococcal vaccines is reduced by bacterial serotypes that are not contained in the vaccine; for example, the seven-valent conjugate vaccine does not cover serotype 1, which might cause 50% of pneumococcal meningitis in parts of Africa.<sup>86,119</sup> The nine-valent vaccine covers serotype 1 and has reduced the incidence of invasive disease in HIV-infected and HIV-uninfected individuals in South Africa and the Gambia.<sup>120,121</sup> Nevertheless, further data about the pneumococcal serotypes that cause meningitis in resource-poor settings are required, and vaccines that contain more serotypes might be more effective. Additionally, the older, cheaper 23-valent polysaccharide vaccine might still have a role in those older than 2 years and in individuals who are HIV negative.<sup>122</sup>

Capsular polysaccharide vaccines to *N meningitidis* serogroups A, C, Y, and W-135 have been available for 30 years; they have been used extensively in the African meningitis belt<sup>107</sup> and could be used effectively in sub-Saharan Africa.<sup>123</sup> A conjugate vaccine to meningococcal serogroup A that has been developed for use in Africa is currently in phase III trials.<sup>107</sup>

### Conclusions

In resource-poor settings, the management of bacterial meningitis is particularly difficult because of factors such as late presentation of the disease, a wide differential diagnosis, and the limited range of diagnostic facilities and therapeutic options. Advances such as the use of diagnostic algorithms, urine dipsticks, and the wider accessibility to ceftriaxone have been made. In the broader context of development, further improvements in

### Search strategy and selection criteria

References for this Review were identified by searches of Medline and PubMed between 1969 and February, 2008, with the term "bacterial meningitis" in conjunction with "diagnosis", "therapy" and "prevention". Abstracts and reports from meetings were not included. The final reference list was generated on the basis of originality and relevance to the aims of the Review.

outcome from bacterial meningitis could be achieved by promoting public awareness of the symptoms and signs of meningitis, by improving access to health-care facilities, and by the development of locally appropriate clinical and laboratory skills. However, the greatest effect on mortality due to bacterial meningitis is likely to be through widespread use of vaccination technology. The implementation of vaccine campaigns on this scale entails considerable organisation, political will, and funding. The Global Alliance for Vaccines and Immunisation (GAVI) was launched in 2000 and aims to garner all of these requirements. In 2006, 22% of the world's birth cohort received a full course of *H influenzae* type-B vaccine compared with only 8% in 1999;<sup>124</sup> a considerable achievement that lends great optimism for the future.

#### Contributors

The authors contributed equally to this Review.

#### Conflicts of interest

We have no conflicts of interest.

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