CURRENT TOPIC

Diagnosis and treatment of bacterial meningitis

H El Bashir, M Laundy, R Booy

Arch Dis Child 2003;**88**:615–620

This review focuses on recent advances of topical interest regarding the diagnosis and treatment of common causes of bacterial meningitis occurring in children beyond the neonatal period. Tuberculous meningitis is beyond the scope of this review.

Bacterial meningitis is an important cause of death both in the developed and developing world.

DIAGNOSIS

Symptoms and signs

Bacterial meningitis can be difficult to diagnose as the symptoms and signs are often non-specific, especially in young children. The symptoms may include high temperature, poor feeding, vomiting, lethargy, and irritability. The clinical signs include bulging fontanelle, fever, drowsiness, apnoeas, convulsions, and purpuric rash. In older children the more classic signs of neck stiffness, headache, and photophobia are more common. The specific signs of Kernig, Brudzinski, and nuchal stiffness are often absent in children.[1] These signs are poorly sensitive in adults, let alone children. In one study in adults, both Kernig and Brudzinski signs had a sensitivity of only 5%, while sensitivity of nuchal rigidity was 30%.[2] The non-specific nature of the symptoms and clinical signs means that we often overtreat and look to other investigations to confirm the diagnosis.

Investigations

Lumbar puncture

Cerebrospinal fluid (CSF) analysis and culture remains the definitive method for diagnosis of meningitis. Issues in respect of indications, contraindications, and safety of lumbar puncture have been covered recently.[3 4]

Whether to perform lumbar puncture (LP) in a child with petechial rash is still a matter of debate. Some in the UK hold that an unwell child with petechial rash is pathognomonic of meningococcal disease and so a lumbar puncture would add very little in terms of diagnosis and carries a high risk of making the haemodynamically unstable child worse.[5 6] Others contend that identification of the organism in the CSF is important for treatment, prophylaxis, and epidemiological studies.[7] We side with the latter view but recognise that there are reasons for delaying LP until it is safe.[3–5] Whether the decision is to perform LP or not, antibiotic treatment should not be delayed.

CSF sterilisation following antibiotic use occurs rapidly. "Sterilisation" of meningococci may occur within two hours, whereas for pneumococci at least four hours of antibiotic therapy is needed.[8] If live bacteria are to be cultured, the LP must be performed before or, if that is not possible, immediately following the administration of antibiotics. The introduction of molecular techniques has, however, meant that live organisms are not required for identification, so there is less need for an early CSF. Blood polymerase chain reaction (PCR) may be negative, whereas PCR performed on CSF collected after treatment and stabilisation can still be informative (see below for further discussion of molecular techniques).

Traditional teaching holds that when white cells found in CSF are primarily polymorphs, meningitis is bacterial in origin. However, viral infections, especially those caused by enterovirus, may initially cause a predominant polymorph response in the CSF, which may persist throughout the illness.[9]

The rapid antigen latex agglutination test on CSF or blood has the benefit that it can be done locally and rapidly, but its lack of sensitivity can limit its clinical use.[10] Ultrasonic enhancement has increased the sensitivity of these tests.[11] Commercial kits are available that cover *Neiserria meningitidis* serogroup B, a combination of meningococcal serogroups (W135, A, C, and Y), *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, *Escherichia coli* K1, and group B streptococcus. Where specimen volume is limited, guiding the microbiology laboratory as to what the clinician thinks is the presumptive infecting organism is important in prioritising the tests.

Cranial computed tomography

Cranial computed tomography (CT) is of limited use in acute bacterial meningitis. It has been used mistakenly to exclude raised intracranial pressure.[12] CT in cerebral oedema may show slit-like lateral ventricles, areas of low attenuation, and absence of basilar and suprachiasmatic cisterns. However, there is considerable variation in the size of normal lateral ventricles, which makes interpretation of the CT scan difficult. There are case reports of cerebral herniation following an LP with a normal CT scan.[13] In a prospective Canadian study of 41 children, clinical management was not influenced by CT findings;

See end of article for authors' affiliations

Correspondence to: Dr H El Bashir, Academic Department of Child Health, 1st Floor, Luckes House, Royal London Hospital, Stepney Way, London E1 1BB, UK; h.elbashir@qmul.ac.uk

Accepted 6 March 2003

Abbreviations: ADH, antidiuretic hormone; CRP, C reactive protein; CSF, cerebrospinal fluid; CT, computed tomography; ECW, extracellular water; ICP, intracranial pressure; IL, interleukin; LP, lumbar puncture; MIC, minimum inhibitory concentration; PAF, platelet activating factor; PCR, polymerase chain reaction; RCT, randomised controlled trial; SIADH, syndrome of inappropriate secretion of antidiuretic hormone; TNF, tumour necrosis factor

those abnormalities detected were already suspected on neurological examination.[14] The main indication for a CT scan in meningitis is when the diagnosis is uncertain and other possible causes of meningism are being considered, for example, posterior fossa tumours or if complications of meningitis are suspected, for example, cerebral abscess. Any decision to perform a CT should not delay the use of antibiotics.

Other investigations

All children admitted to hospital with suspected meningitis should have a blood culture, a throat swab, a blood EDTA (ethylenediaminetetra-acetic acid) specimen for PCR studies and baseline clotted blood for serology. Full blood count, C reactive protein (CRP), clotting studies, and urea and electrolytes should also be routinely performed. A trap to watch for is a low or normal CRP that may occur early in severe infection.

Meningococci can be isolated from the throat in about half the patients with meningococcal disease; this figure is not affected by antibiotic treatment.[15]

Aspiration of petechiae in meningococcal disease is a neglected investigation. One study found that petechiae from two thirds of patients contain meningococci, which could be seen on Gram stain or cultured.[16] Antibiotics do not affect the visualisation of meningococci in the skin aspirates.[17] This investigation is particularly useful in that a definitive diagnosis of meningococcal disease can be made when clinical signs preclude lumbar puncture.

Molecular techniques

PCR for *Neisseria meningitidis* and *Streptococcus pneumoniae* using either blood or CSF can be obtained in the UK from several public health laboratories. In the case of meningococcus, the introduction of a new extraction method from whole blood has improved sensitivity and specificity of PCR; in a recent study from Liverpool a sensitivity of 87% and a specificity of 100% were reported in children with probable meningococcal disease.[18] The clinical distinction of probable from possible meningococcal disease is important, as the yield from patients described as "possible" cases is very low. Requesting PCR tests on samples from every patient with the remotest chance of meningococcal disease would lead to inundation of the diagnostic service with very little benefit.[19] It may be argued that if the clinician is already certain that he or she is dealing with meningococcal disease, why the need for further tests? However, confirmation is important at an epidemiological and public health level, especially as PCR techniques can be used to further characterise meningococci, for example, by serogroup and serotype.[20] Furthermore, not all ill children with haemorrhagic rash have meningococcal disease. While the test itself can be done quickly in the UK (and elsewhere) on the same day of receipt, the centralised nature of the service in the UK at the Meningococcal Reference Unit means that, once transport time is factored in, the turnaround may be several days before a result is available.

PCR may in the future be used to determine prognosis. A recent study using quantitative PCR on blood revealed that meningococcal bacterial DNA load correlates with disease severity and that the maximum load is highest in those who die.[21]

For the diagnosis of pneumococcal disease, using PCR may be problematic. Its role in diagnosis is at present not as well established as for meningococci. Most commonly, the technique involves the amplification of the pneumolysin gene common to all pneumococci. On CSF, the test is both sensitive and specific.[22] However on blood, false positive results may be obtained due to the high nasopharyngeal carriage rate in young children.[23]

TREATMENT

The choice of antibiotic depends on the organism isolated. In most cases the initial treatment has to be empirical, but nonetheless based on epidemiological knowledge of the commonest organisms for each age group and local antibiotic resistance patterns. The chosen antibiotic should have bactericidal activity in the CSF. Patients with pneumococcal or Gram negative bacillary meningitis who are treated with bacteriostatic antibiotics may have a poor clinical outcome.[24] Animal studies have shown that a bactericidal effect is necessary for sterilisation of the CSF and survival.[25]

There are three factors affecting antibiotic activity: ability to penetrate the CSF, concentration, and intrinsic activity in infected fluid.[26 27] When the blood-brain barrier is intact, penetration is limited, because transport across cells is minimal and the junctions between endothelial cells of the cerebral microvasculature are tight. In meningitis, the integrity of the barrier is altered, resulting in increased permeability and enhanced CSF penetration of most antibiotics. The antibiotic concentration in CSF needed for optimal bactericidal activity is uncertain. However, in experimental studies, maximal bactericidal activity occurs when the concentration of an antibiotic is approximately 10–30 times the minimal bactericidal concentration against the organism in vitro.[28 29]

Bactericidal antibiotics promote the release of bacteria cell wall products such as endotoxins, teichoic acid, and peptidoglycans. These products provoke the production of the inflammatory mediators such as tumour necrosis factor α (TNF-α), interleukin 1 (IL-1), and platelet activating factor (PAF). The release of inflammatory mediators can be associated with worsening of disease and poor outcome. However, one experimental study showed that the release of bacterial toxins after initiation of antibiotics was much less than that released by bacteria not exposed to antibiotics.[30]

In a child with suspected meningitis, urgent transfer to hospital, followed by concurrent microbiological investigation and antibiotic treatment are the cornerstones of management.

Lack of adequate blood and CSF culture may result in difficulty deciding on the duration of treatment and uncertainty over the antimicrobial susceptibility of the organism.

Partially treated meningitis

As the early symptoms and signs of bacterial meningitis are non-specific, up to 50% of cases may initially receive oral antibiotics.[31] This partial treatment may delay the child's presentation to hospital and result in a diagnostic dilemma. The CSF findings may be altered; Gram stain and growth of organism may be negative, however antibiotics rarely interfere with CSF protein or glucose. In this situation CSF should be sent for both PCR and bacterial antigen detection, as these are not affected by prior antibiotic administration.[31]

Duration of treatment and choice of antibiotic

The duration of antibiotic therapy depends on the organism isolated. For *S pneumoniae* and *H influenzae*, 10–14 days treatment is generally recommended while for *N meningitidis* a seven day course is sufficient. In *Listeria monocytogenes* and group B streptococcal meningitis, antibiotics should be given for 14–21 days. For Gram negative bacilli a minimum of three weeks is needed.[32]

In most cases of bacterial meningitis a broad spectrum cephalosporin (cefotaxime or ceftriaxone) is the most appropriate empirical choice in children over 3 months old. These cover *Neisseria meningitides*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*, and penetrate CSF well. Ampicillin should be added in young infants (less than 3 months old) to cover *Listeria monocytogenes.* The treatment of choice for Gram negative bacillary meningitis is cefotaxime or ceftriaxone. Aminoglycosides are sometimes used in addition, but not alone as they often do not exceed the minimum inhibitory concentrations (MIC) for Gram negative bacteria and may not be successful in eradicating the pathogen.

Ceftriaxone may be effective when given as a single daily dose (80–100 mg/kg) to treat serious bacterial infections

Table 1 Dosages and frequency of the common antibiotics used in bacterial meningitis

Drug	Dose	Frequency (times daily)	Maximum total daily dose
Penicillin G	50 mg/kg	4–6	14.4 g
Cefotaxime	50 mg/kg	4	3 g
Ceftriaxone	80–100 mg/kg	1	4 g
Ampicillin	100 mg/kg	4	3 g
Ceftazidime	50 mg/kg	3	6 g
Vancomycin	15 mg/kg then 10 mg/kg	4	2 g

including meningitis in children.[33] Although this regimen may be cost effective, safe, and convenient, one concern is that missing a single dose or delaying it may result in inadequate CSF drug concentration. A randomised trial in 100 infants who were already showing signs of recovery revealed that four days of ceftriaxone treatment is as effective as seven days with no difference in complications.[34] We suggest that confirmation is required from larger studies of these encouraging results before recommending a shorter treatment period.

Antibiotic therapy may need to be modified once a pathogen is cultured and antibiotic susceptibility testing becomes available. If pneumococcal meningitis is high on the differential diagnosis and there is a clear history of anaphylaxis to β lactams, and keeping in mind that perhaps 10% of those allergic to penicillin cross react to cephalosporin, a combination of vancomycin and chloramphenicol is an alternative. Vancomycin is added because of the risk of penicillin resistant pneumococci and the possibility of failure of chloramphenicol in this group.[35]

For more complicated cases such as immunosuppressed patients or those with recent history of head trauma or neurosurgery, and those with cerebrospinal fluid shunts, broad spectrum antibiotics against Gram positive and Gram negative organisms should be given, such as a combination of vancomycin and ceftazidime.[32]

Studies comparing the use of rifampicin with ceftriaxone in experimental *S pneumoniae* meningitis support the use of rifampicin because of a reduction in the release of proinflammatory mediators, decreased secondary brain injury, and a lower early mortality rate.[36 37] As the release of bacterial cell wall products and the production of proinflammatory mediators may be associated with more severe disease and worse outcome in some patients with bacterial meningitis, the initial use of rifampicin (for say 1–2 hours) followed by addition of a β lactam may result in reduction of tissue damage and a better outcome. However this approach is not human evidence based.

Other less frequently used carbapenem antibiotics, such as imipenem and meropenem, are very active in vitro against most isolates of *S pneumoniae*, although some penicillin resistant strains have shown reduced susceptibility.[38] Fluroquinolones, such as trovafloxacin, gatifloxacin, and moxifloxacin are potentially effective in the treatment of multiply resistant pneumococcal isolates because of their activity and CSF penetration, even when dexamethasone is also given.[39 40]

Table 1 shows the dosages and the frequency of the common antibiotics used.

Antibiotic resistance

There has been a worldwide increase reported in infection with penicillin and cephalosporin resistant strains of *S pneumoniae*, for example in Europe, South Africa, Asia, and the United States.[41–45] The rate in the UK remains low but has increased.[46] Such meningitis may not respond to high dose penicillin therapy and those resistant to cephalosporin may not respond to the standard dose.[47] The resistance of *S pneumoniae* to penicillin and other β lactam antibiotics is caused by either alteration in the penicillin binding proteins involved in the synthesis of bacterial cell wall or the production of β lactamase.[48] In view of the increasing reports of resistant strains of *S pneumoniae* in the United States, the American Academy of Pediatrics recommended combination therapy, initially with vancomycin and either cefotaxime or ceftriaxone for all children 1 month of age or older with definite or probable bacterial meningitis. Studies in adults have shown that vancomycin should not be used alone in resistant cases as there are doubts about its penetration into the CSF, especially in those given dexamethasone concurrently.[49 50] A recent study in children showed that vancomycin need not be given if LP is done early and Gram positive diplococci are not seen on Gram stain.[51] We suggest that in the majority of UK centres where cephalosporin resistance remains at very low levels, empirical use of vancomycin is not necessary. Where vancomycin is used empirically, it should be discontinued if the organism is later shown to be susceptible to penicillin, or to cefotaxime or ceftriaxone.[52]

In the case of *N meningitidis* isolates, the great majority are susceptible to penicillin and ampicillin, although strains with reduced susceptibility have been reported in Europe, South Africa, and the United States.[53] Such resistant strains usually respond to the standard high dose of penicillin recommended for meningitis.[54]

Use of intravenous fluids

In general, most children admitted with meningitis are given intravenous fluids. A common practice has been to restrict fluids to two thirds or three quarters of the daily maintenance: the reasoning is that this reduces the likelihood of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). The incidence of SIADH reported in studies varies considerably, from 4% to 88%, which can be attributed to the different criteria used in its definition. SIADH leads to hyponatraemia and fluid retention, which may worsen cerebral oedema. However, a significant proportion of meningitis cases present with dehydration or hypovolaemia and are in clinical need of fluid resuscitation.[55] As the mechanism of antidiuretic hormone (ADH) secretion in meningitis is still unknown, the debate on whether the increased secretion of ADH is appropriate or not, remains unclear. This has resulted in the clinical dilemma of whether fluids should be restricted or not. Children with meningitis have excess total and extracellular water (ECW), an appropriate increased secretion of ADH, and mild systemic hypertension. All these changes are needed to overcome the raised intracranial pressure and to maintain adequate cerebral blood flow and perfusion. Consequently fluid restriction may increase the likelihood of adverse outcome.[56] One experimental study showed that liberal fluid administration in *Escherichia coli* meningitis did not aggravate brain oedema.[57] Interestingly, a recent multicentre randomised trial from Papua New Guinea comparing moderate oral fluid restriction to total maintenance intravenous fluids in the first 48 hours in children, did not show any increase in adverse outcome in the non-restricted group; however, signs of dehydration at presentation were a risk factor for adverse outcome

in the fluid restricted group.[58] Hyponatraemia has been correlated with an increased risk of seizures and neurological abnormalities.[59] Although hyponatraemia can occur as a result of excessive fluid administration or SIADH, it can also occur in children with dehydration.[60] It is therefore important that the degree of hydration is carefully assessed in order to correctly manage the fluid balance. If the decision is not to restrict fluid intake, extra care should be taken to avoid over-hydration, as this can easily occur inadvertently when maintenance fluids are given intravenously and other oral intake (for example, breast feeding) is allowed.[57]

The British Infection Society working party recommended that adult patients with meningitis should be kept euvolaemic and not fluid restricted in an attempt to reduce cerebral oedema.[35] Similarly we suggest that the evidence does not support fluid restriction in children.

Use of dexamethasone

Steroids have anti-inflammatory effects and decrease the release of various cytokines. They inhibit the transcriptions of mRNA for TNF-α and IL-1, and the production of prostaglandins and PAF, reduce vasogenic cerebral oedema, and reduce the production of inducible nitric oxide synthase.[61–63] Inflammatory changes in meningitis may ultimately lead to nerve damage and deafness. The use of corticosteroids in bacterial meningitis has been debated for more than 40 years.[64] Recent meta-analyses of steroid use in bacterial meningitis have reached different conclusions, perhaps because of the difference in their eligibility criteria.[65 66] A study showed that conclusions derived from some of the randomised controlled trials (RCTs) of antibiotic use in bacterial meningitis may be inaccurate because they are underpowered to show clinically significant differences.[67] We can speculate that the same has occurred with RCTs of steroid use in meningitis. This may explain why some RCTs have shown that dexamethasone reduces overall mortality, hearing loss, and the incidence of long term neurological sequelae in children, whereas others did not show similar benefits.[66 68–70]

Different doses of dexamethasone have been used. A dose of 0.4 mg/kg given every 12 hours for a total duration of two days proved to be safe and as efficacious as the dose of 0.15 mg/kg given every six hours for four days.[71] The short course may perhaps help to reduce the risk of gastric haemorrhage.

There are concerns regarding the penetration of antibiotics into the CSF when steroids are used. Animal studies showed that penetration of antibiotics such as vancomycin is reduced in steroid treated compared with non-steroid treated animals. However in children, vancomycin achieved adequate concentration in the CSF even when dexamethasone was concurrently given.[72 73]

A recent large double blind placebo controlled trial from Malawi showed no benefit of dexamethasone as an adjuvant treatment in children with acute bacterial meningitis in a developing country. Delayed presentation and underling illnesses such as anaemia, malnutrition, and HIV-1 infection may have influenced the effect of dexamethasone in this setting.[74]

The best evidence for the benefits of dexamethasone is in *H influenzae* type b meningitis. However, the evidence of benefit for pneumococcal meningitis is less certain. There does appear to be benefit if dexamethasone is commenced before or simultaneously with the antibiotic.[71 75] We favour its use empirically in developed countries for children with suspected meningitis.

As a result of the changing epidemiology of bacterial meningitis, for example, the massive reduction in *H influenzae* type b meningitis and the emergence of antibiotic resistance, the question of the efficacy of steroids in bacterial meningitis will continue to be debated.

Recommendations for prevention of secondary cases among close contacts

***H influenzae* type b infection**

- All home contacts should be given rifampicin 20 mg/kg/day (max. 600 mg/day) for four days.
- Any unvaccinated children aged 12–48 months, should be given one dose of the vaccine.
- Unvaccinated children aged 2–11 months should be given three doses of the vaccine.

Meningococcal infection *(should be given one* of the following)

- Rifampicin 600 mg every 12 hours for two days for adults; for children the dose is 10 mg/kg (under 1 year, 5 mg/kg) every 12 hours for two days orally.
- Ceftriaxone 250 mg in adults (child <12 years, 125 mg) intramuscularly as a single dose.
- Ciprofloxacin 500 mg orally as a single dose in adults and children aged >12 years (not licensed but extensively used).
- Unvaccinated children and close contacts aged >2 years and exposed to meningococcus A, C, Y, or W135, should be offered quadrivalent meningococcal vaccine.[79]

For details of those who should receive chemoprophylaxis, contact a consultant in communicable disease control (or a consultant in infectious diseases, or the local public health laboratory).

Unless there has been mouth-to-mouth contact (or direct exposure to infectious droplets from a patient with meningococcal disease), healthcare workers do not generally require chemoprophylaxis

Pneumococcal meningitis

- Chemoprophylaxis not normally indicated for close contacts.

Other types of bacterial meningitis

- Secondary prevention not required.

Treatment of raised intracranial pressure

Raised intracranial pressure (ICP) is a well recognised complication of meningitis. The signs of raised ICP include altered level of consciousness, bradycardia, hypertension or hypotension, and altered respiratory pattern. A normal fundoscopy examination does not rule out a raised ICP, as papilloedema is a late sign.

Osmotic diuretics such as 20% mannitol, glycerol, and hypertonic saline are used in the treatment of cerebral oedema and raised ICP. Their action is through shifting fluids from the extravascular to the intravascular space, resulting in a reduction of intracranial pressure. Mannitol is given as an infusion in a dose of 0.25–1 g/kg. Mannitol is not without side effects; a hyperosmolar state may follow repeated doses, worsening cerebral oedema and impairing cardiac output.[76]

No published evidence is yet available, but there is a randomised controlled trial of glycerol, mannitol, and steroids in the treatment of raised ICP for children with bacterial meningitis, which will close in 2004 (Heikki Peltola, personal communication).

Measures to optimise brain homoeostasis by ensuring adequate delivery of oxygen and nutrients as well as maintaining cerebral perfusion and ensuring adequate mean arterial pressure are as essential as interventions to reduce raised ICP.[77] Such interventions range from nursing the child in a head up position of 20–30° and in a quiet environment, to elective intubation and sedation and appropriate treatment, to lower intracranial pressure.[76 77] The beneficial effect of hyperventilation in the treatment of raised ICP is still debated. It is generally recommended to aim for a minimal hypocapnia ($PaCO_2$ not less than 3.5 kPa) to avoid excessive cerebral vasoconstriction.

Chemoprophylaxis and prevention of secondary cases

There are no published systematic reviews or randomised controlled trials studying the effect of prophylactic antibiotics in preventing subsequent cases in meningococcal disease. An RCT that is large enough to find a significant difference is unlikely to be performed. One RCT showed benefit of rifampicin in preventing secondary cases of *Haemophilus influenzae* meningitis among close contacts.[78]

Suspected cases should be reported as soon as possible to the local public health services, and general practitioners should be informed about policies for secondary prevention of cases.[35]

The box gives recommendations for chemoprophylaxis and prevention of secondary cases among close contacts.

ACKNOWLEDGEMENTS

We are grateful to Drs DV Shingadia, P Heath, E Price, and E Kaczmarski for helpful comments on drafts of this paper.

Authors' affiliations

H El Bashir, M Laundy, R Booy, Academic Department of Child Health, Queen Mary School of Medicine and Dentistry at Barts and The London, University of London, UK

REFERENCES

1 **Radetsky M**. Duration of symptoms and outcome in bacterial meningitis: an analysis of causation and the implications of a delay in diagnosis. *Pediatr Infect Dis J* 1992;**11**:694–8.
2 **Thomas KE**, Hasbun R, Jekel J, *et al*. The diagnostic accuracy of Kernig's sign, Brudzinski's sign, and nuchal rigidity in adults with suspected meningitis. *Clin Infect Dis* 2002;**35**:46–52.
3 **Kneen R**, Solomon T, Appleton R. The role of lumbar puncture in suspected CNS infection—a disappearing skill? *Arch Dis Child* 2002;**87**:181–3.
4 **Riordan FAI**, Cant AJ. When to do a lumbar puncture. *Arch Dis Child* 2002;**87**:235–7.
5 **Nadel S**. Lumbar puncture should not be performed in meningococcal disease. *Arch Dis Child* 2001;**84**:375.
6 **Addy DP**. When not to do a lumbar puncture. *Arch Dis Child* 1987;**62**:873–5.
7 **Sam WI**. The role of lumbar puncture in meningococcal disease. *Arch Dis Child* 2000;**83**:370.
8 **Kanegaye JT**, Soliemanzadeh P, Bradley JS. Lumbar puncture in pediatric bacterial meningitis: defining the time interval for recovery of cerebrospinal fluid pathogens after parenteral antibiotic pretreatment. *Pediatrics* 2001;**108**:1169–74.
9 **Negrini B**, Kelleher KJ, Wald ER. Cerebrospinal fluid findings in aseptic versus bacterial meningitis. *Pediatrics* 2000;**105**:316–19.
10 **Perkins MD**, Mirrett S, Reller LB. Rapid bacterial antigen detection is not clinically useful. *J Clin Microbiol* 1995;**33**:1486–91.
11 **Barnes RA**, Jenkins P, Coakley WT. Preliminary clinical evaluation of meningococcal disease and bacterial meningitis by ultrasonic enhancement. *Arch Dis Child* 1998;**78**:58–60.
12 **Haslam RH**. Role of computed tomography in the early management of bacterial meningitis. *J Pediatr* 1991;**119**:157–9.
13 **Shetty AK**, Desselle BC, Craver RD, *et al*. Fatal cerebral herniation after lumbar puncture in a patient with a normal computed tomography scan. *Pediatrics* 1999;**103**:1284–7.
14 **Cabral DA**, Flodmark O, Farrell K, *et al*. Prospective study of computed tomography in acute bacterial meningitis. *J Pediatr* 1987;**111**:201–5.
15 **Cartwright K**, Kroll S. Optimising the investigation of meningococcal disease. *BMJ* 1997;**315**:757–8.
16 **van Deuren M**, van Dijke BJ, Koopman RJ, *et al*. Rapid diagnosis of acute meningococcal infections by needle aspiration or biopsy of skin lesions. *BMJ* 1993;**306**:1229–32.
17 **Taylor MR**, Keane CT, Periappuram M. Skin scraping is a useful investigation in meningococcal disease. *BMJ* 1997;**314**:831–2.
18 **Hackett SJ**, Carrol ED, Guiver M, *et al*. Improved case confirmation in meningococcal disease with whole blood Taqman PCR. *Arch Dis Child* 2002;**86**:449–52.
19 **Carrol ED**, Thomson AP, Shears P, *et al*. Performance characteristics of the polymerase chain reaction assay to confirm clinical meningococcal disease. *Arch Dis Child* 2000;**83**:271–3.
20 **Borrow R**, Claus H, Guiver M, *et al*. Non-culture diagnosis and serogroup determination of meningococcal B and C infection by a sialyltransferase (siaD) PCR ELISA. *Epidemiol Infect* 1997;**118**:111–17.
21 **Hackett SJ**, Guiver M, Marsh J, *et al*. Meningococcal bacterial DNA load at presentation correlates with disease severity. *Arch Dis Child* 2002;**86**:44–6.
22 **Cherian T**, Lalitha MK, Manoharan A, *et al*. PCR-enzyme immunoassay for detection of Streptococcus pneumoniae DNA in cerebrospinal fluid samples from patients with culture-negative meningitis. *J Clin Microbiol* 1998;**36**:3605–8.
23 **Dagan R**, Shriker O, Hazan I, *et al*. Prospective study to determine clinical relevance of detection of pneumococcal DNA in sera of children by PCR. *J Clin Microbiol* 1998;**36**:669–73.
24 **Cherubin CE**, Marr JS, Sierra MF, *et al*. Listeria and gram-negative bacillary meningitis in New York City, 1972–1979: frequent causes of meningitis in adults. *Am J Med* 1981;**71**:199–209.
25 **Scheld WM**, Sande MA. Bactericidal versus bacteriostatic antibiotic therapy of experimental pneumococcal meningitis in rabbits. *J Clin Invest* 1983;**71**: 411–19.
26 **Sande MA**. Factors influencing the penetration and activity of antibiotics in experimental meningitis. *J Infect* 1981;**3**(suppl):33–8.
27 **Tauber MG**, Sande MA. General principles of therapy of pyogenic meningitis. *Infect Dis Clin North Am* 1990;**4**:661–76.
28 **Tauber MG**, Doroshow CA, Hackbarth CJ, *et al*. Antibacterial activity of beta-lactam antibiotics in experimental meningitis due to Streptococcus pneumoniae. *J Infect Dis* 1984;**149**:568–74.
29 **Strausbaugh LJ**, Sande MA. Factors influencing the therapy of experimental Proteus mirabilis meningitis in rabbits. *J Infect Dis* 1978;**137**:251–60.
30 **Friedland IR**, Jafari H, Ehrett S, *et al*. comparison of endotoxins release by different antimicrobial agents and the effect of inflammation in experimental Escherichia coli meningitis. *J Infect Dis* 1993;**168**:657–62.
31 **Behrman RE**, Kliegman RM, Arvin AM. *Nelson textbook of pediatrics*, 15th edn. W B Saunders, 1996.
32 **Quagliarello VJ**, Scheld WM. Treatment of bacterial meningitis. *N Engl J Med* 1997;**336**:708–16.
33 **Frenkel LD**, and the Multicentre Ceftriaxone Pediatric Study Group. Once-daily administration of ceftriaxone for the treatment of selected bacterial infections in children. *Pediatrics* 1988;**82**:486–91.
34 **Roine I**, Ledermann W, Foncea LM, *et al*. Randomised trial of four vs. seven days of ceftriaxone treatment for bacterial meningitis in children with rapid initial recovery. *Pediatr Infect Dis J* 2000;**19**:219–22.
35 **Begg N**, Cartwright KA, Cohen J, *et al*. Consensus statement on diagnosis, investigation, treatment and prevention of acute bacterial meningitis in immunocompetent adults. *J Infect* 1999;**39**:1–15.
36 **Bottcher T**, Gerber J, Wellmer A, *et al*. Rifampin reduces production of reactive oxygen species of cerebrospinal fluid phagocytes and hippocampal neuronal apoptosis in experimental Streptococcus pneumoniae meningitis. *J Infect Dis* 2000;**181**:2095–8.
37 **Nau R**, Wellmer A, Soto A, *et al*. Rifampin reduces early mortality in experimental Streptococcus pneumoniae meningitis. *J Infect Dis* 1999;**179**:1557–60.
38 **Pikis A**, Donkersloot JA, Akram S, *et al*. Decreased susceptibility to imipenem among penicillin-resistant Streptococcus pneumoniae. *J Antimicrob Chemother* 1997;**40**:105–8.
39 **Paris MM**, Hickey S, Uscher MI, *et al*. Evaluation of CP-99,219, a new fluoroquinolone, for the treatment of experimental penicillin- and cephalosporin-resistant pneumococcal meningitis. *Antimicrob Agents Chemother* 1995;**39**:1243–6.
40 **Schmidt H**, Dalhoff A, Stuertz K, *et al*. Moxifloxacin in the therapy of experimental pneumococcal meningitis. *Antimicrob Agents Chemother* 1998;**42**:1397–407.
41 **Fenoll A**, Martin Bourgon C, Munoz R, *et al*. Serotype distribution and antimicrobial resistance of Streptococcus pneumoniae isolates causing systemic infections in Spain, 1979–1989. *Rev Infect Dis* 1991;**13**:56–60.
42 **Marton A**, Gulyas M, Munoz R, *et al*. Extremely high incidence of antibiotic resistance in clinical isolates of Streptococcus pneumoniae in Hungary. *J Infect Dis* 1991;**163**:542–8.
43 **Friedland IR**, Klugman KP. Antibiotic-resistant pneumococcal disease in South African children. *Am J Dis Child* 1992;**146**:920–3.
44 **Yoshida R**, Kaku M, Kohno S, *et al*. Trends in antimicrobial resistance of Streptococcus pneumoniae in Japan. *Antimicrob Agents Chemother* 1995;**39**:1196–8.
45 **Jones RN**, Kehrberg E, Erwin ME, *et al*. Epidemiologic studies of emerging antimicrobial resistance in USA hospitals: report from a forty medical centre surveillance of parenteral drug susceptibility. In: *Program and abstracts of the 34th Interscience Conference on Antimicrobial Agents and Chemotherapy, Orlando, FL, 4–7 October 1994*. Washington, DC: American Society for Microbiology, 1994:87.
46 **Reacher MH**, Shah A, Livermore DM, *et al*. Bacteraemia and antibiotic resistance of its pathogens reported in England and Wales between 1990 and 1998: trend analysis. *BMJ* 2000;**320**:213–16.
47 **Friedland IR**, McCracken GH. Management of infections caused by antibiotic resistant Streptococcus pneumoniae. *J Infect Dis* 1984;**149**:568–74.
48 **Coffey TJ**, Daniels M, McDougal LK, *et al*. Genetics analysis of clinical isolates of Streptococcus pneumoniae with high level resistance to expanded-spectrum cephalosporins. *Antimicrob Agents Chemother* 1995;**39**:1306–13.
49 **Viladrich PF**, Gudiol F, Linares J, *et al*. Evaluation of vancomycin for therapy of adult pneumococcal meningitis. *Antimicrob Agents Chemother* 1991;**35**:2467–72.
50 **Friedland IR**, Paris M, Ehertt S, *et al*. Evaluation of antimicrobial regimens for treatment of experimental penicillin and cephalosporin-resistant pneumococcal meningitis. *Antimicrob Agents Chemother* 1993;**37**:1630–6.
51 **McMaster P**, McIntyre P, Gilmour R, *et al*. The emergence of resistant pneumococcal meningitis—implications for empiric therapy. *Arch Dis Child* 2002;**87**:207–11.
52 **American Academy of Pediatrics**. Pneumococcal infections. In: Pickering LK, ed. *Red Book: Report of the Committee on Infectious Diseases*, 25th edn. Elk Grove Village, IL: American Academy of Pediatrics, 2000:452–60.

53 **Dillon JR**, Pauze M, Yeung K-H. Spread of penicillinase-producing and transfer plasmids from gonococcus to Neisseria meningitidis. *Lancet* 1983;**1**:779–81.
54 **Woods CR**, Smith AL, Wasilauskas BL, *et al*. Invasive disease caused by Neisseria meningitidis relatively resistant to penicillin in North Carolina. *J Infect Dis* 1994;**170**:453–6.
55 **Prince AS**, Neu HC. Fluid management in Hameophilus influenzae meningitis. *Infection* 1980;**8**:5–7.
56 **Singhi SC**, Singhi PD, Srinivas B, *et al*. Fluid restriction does not improve the outcome of acute meningitis. *Pediatr Infect Dis J* 1995;**14**:495–503.
57 **Tauber MG**, Sande E, Fournier MA, *et al*. Fluid administration, brain oedema, and cerebrospinal fluid lactate and glucose concentration in experimental Escherichia coli meningitis. *J Infect Dis* 1993;**168**:473–6.
58 **Duke T**, Mokela D, Frank D, *et al*. Management of meningitis in children with oral fluid restriction or intravenous fluid at maintenance volumes: a randomised trial. *Ann Trop Paediatr* 2002;**22**:145–57.
59 **Kaplan SL**, Feigin RD. The syndrome of inappropriate secretion of antidiuretic hormone in children with bacterial meningitis. *J Pediatr* 1978;**92**:758–61.
60 **Bianchetti MG**, Thyssen HR, Laux-End R, *et al*. Evidence for fluid volume depletion in hyponatraemic patients with bacterial meningitis. *Acta Paediatr* 1996;**85**:1163–6.
61 **Kato K**, Yokoi T, Takano N, *et al*. Detection by in situ hybridisation and phenotypic characterisation of cells expressing IL-6 m RNA in human stimulated blood. *J Immunol* 1990;**144**:1317–22.
62 **Fishman RA**. Steroids in the treatment of brain edema. *N Engl J Med* 1982;**306**:359–60.
63 **Moncada S**, Palmer RM, Higgs EA. Nitric oxide: physiology, pathophysiology, and pharmacology. *Pharmacol Rev* 1991;**43**:109–42.
64 **Lepper MH**, Spies HW. Treatment of pneumococci meningitis. *Arch Intern Med* 1958;**104**:252–9.
65 **Havens P**, Wendelberger KJ, Hofman GM, *et al*. Corticosteroid as adjunctive therapy in bacterial meningitis. *Am J Dis Child* 1989;**143**:1051–5.
66 **Geiman BJ**, Smith AL. Dexamethasone and bacterial meningitis: a meta-analysis of randomised controlled trials. *West J Med* 1992;**157**:27–31.
67 **Krysan D**, Kemper AR. Claims of equivalence in randomized controlled trials of the treatment of bacterial meningitis in children. *Pediatr Infect Dis J* 2002;**21**:753–7.
68 **Kennedy WA**, Hoyt MJ, McCracken GH Jr. The role of corticosteroid therapy in children with pneumococcal meningitis. *Am J Dis Child* 1991;**145**:1374–8.
69 **Kanra GY**, Ozen H, Secmeer G, *et al*. Beneficial effects of dexamethasone in children with pneumococcal meningitis. *Pediatr Infect Dis J* 1995;**14**:490–4.
70 **Girgis NI**, Farid Z, Mikhail IA, *et al*. Dexamethasone treatment for bacterial meningitis in children and adults. *Pediatr Infect Dis J* 1989;**6**:848–51.
71 **Schaad UB**, Lips U, Gnehm HE, *et al*. Dexamethasone therapy for bacterial meningitis in children. *Lancet* 1993;**342**:457–61.
72 **Friedland IR**, Paris MM, Ehrett S, *et al*. Evaluation of antimicrobial regimens for treatment of experimental penicillin- and cephalosporin-resistant pneumococcal meningitis. *Antimicrob Agents Chemother* 1993;**37**:1630–6.
73 **Klugman KP**, Friedland IR, Bradley JS. Bactericidal activity against cephalosporin-resistant Streptococcus pneumoniae in cerebrospinal fluid of children with acute bacterial meningitis. *Antimicrob Agents Chemother* 1995;**39**:1988–92.
74 **Molyneux EM**, Walsh AL, Forsyth H, *et al*. Dexamethasone treatment in childhood bacterial meningitis in Malawi: a randomised controlled trial. *Lancet* 2002;**360**:211–17.
75 **McIntyre PB**, Berkey CS, King SM, *et al*. Dexamethasone as adjunctive therapy in bacterial meningitis. A meta-analysis of randomized clinical trials since 1988. *JAMA* 1997;**278**:925–31.
76 **Levin M**, Walters MDS. Infections of the nervous system. In: Brett EM, ed. *Paediatric neurology*, 3rd edn. Edinburgh: Churchill Livingstone, 1997:632–3.
77 **Pickard JD**, Czosnyka M. Raised intracranial pressure. In: Hughes RAC, ed. *Neurological emergencies*, 3rd edn. London: BMJ Publishing Group, 2000:173–218.
78 **Band JD**, Fraser DW, Ajello G, Haemophilus Influenzae Disease Study Group. Prevention of Haemophilus influenzae type b disease. *JAMA* 1984;**251**:2381–6.
79 **Public Health Laboratory Service Meningococcus Forum**. Guidelines for public health management of meningococcal disease in the UK. *Commun Dis Public Health* 2002;**5**:184–204.