EFNS GUIDELINES/CME ARTICLE

EFNS guideline on the management of community-acquired bacterial meningitis: report of an EFNS Task Force on acute bacterial meningitis in older children and adults

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Acute bacterial meningitis (ABM) is a potentially life-threatening neurological emergency. An agreed protocol for early, evidence-based and effective management of community-acquired ABM is essential for best possible outcome. A literature search of peer-reviewed articles on ABM was used to collect data on the management of ABM in older children and adults. Based on the strength of published evidence, a consensus guideline was developed for initial management, investigations, antibiotics and supportive therapy of community-acquired ABM. Patients with ABM should be rapidly hospitalized and assessed for consideration of lumbar puncture (LP) if clinically safe. Ideally, patients should have fast-track brain imaging before LP, but initiation of antibiotic therapy should not be delayed beyond 3 h after first contact of patient with health service. In every case, blood sample must be sent for culture before initiating antibiotic therapy. Laboratory examination of cerebrospinal fluid is the most definitive investigation for ABM and whenever possible, the choice of antibiotics, and the duration of therapy, should be guided by the microbiological diagnosis. Parenteral therapy with a third-generation cephalosporin is the initial antibiotics of choice in the absence of penicillin allergy and bacterial resistance; amoxicillin should be used in addition if meningitis because of *Listeria monocytogenes* is suspected. Vancomycin is the preferred antibiotic for penicillin-resistant pneumococcal meningitis. Dexamethasone should be administered both in adults and in children with or shortly before the first dose of antibiotic in suspected cases of *Streptococcus pneumoniae* and *H. Influenzae* meningitis. In patients presenting with rapidly evolving petechial skin rash, antibiotic therapy must be initiated immediately on suspicion of *Neisseria meningitidis* infection with parenteral benzyl penicillin in the absence of known history of penicillin allergy.

Objectives

The primary objective of this guideline is to assist neurologists with the diagnosis and treatment of community-acquired acute bacterial meningitis (ABM) in older children and adults based on literature evidence and expert consensus. Here, we propose early diagnosis and treatment of ABM, as soon as possible, and a target time of no longer than 3 h from door-to-first antibiotic therapy based on secured diagnosis supported by clinical and cerebrospinal fluid (CSF) findings. The management of hospital acquired ABM and chronic meningitis, tuberculous meningitis inclusive, is not considered in this document.

Short Version: This is an abridged, print version of the guideline. The full version, with complete list of reference and tables, is available at the *EJoN* website–see Supplementary material.

This is a Continuing Medical Education article, and can be found with corresponding questions on the internet at http://www.efns.org/content.php?pid = 132. Certificates for correctly answering the questions will be issued by the EFNS.

Search strategy and selection criteria

Data for this guideline were identified by searches of MEDLINE, EMBASE, the Cochrane databases and references from relevant articles. Search terms used were (alone and in combination): bacterial meningitis,

meningococcal meningitis, pneumoccal meningitis, Listeria meningitis and meningoencephalitis, lumbar puncture (LP), CSF, treatment for meningitis, antibiotic, dexamethasone and vaccine. For determining the levels of evidence for therapeutic interventions, the EFNS guideline was followed [1] (Table S1). Only research papers published in English were considered. Limitations of the search strategy include: non-randomized clinical data, lack of sensitivity and specificity, small numbers of cohorts and case–control studies.

Background

Acute bacterial meningitis is a life-threatening neurological emergency. Its estimated annual incidence is 2–5 per 100 000 people in the Western world and a figure that may be 10 times as high in the less developed countries [w1]. ABM is one of top 10 causes of infection-related death worldwide [w2] and 30–50% of its survivors have permanent neurological sequelae [w3,w4]. The causative organism of ABM can be reliably predicted by the age of the patient, predisposing factors, underlying diseases and immunological competence. *Streptococcus pneumoniae* and *Neisseria meningitidis* are the two most common aetiologic agents of ABM in immunocompetent infants (> 4 weeks) and children, as well as in adults, comprising nearly 80% of all cases, followed by *Listeria monocytogenes* and staphylococci (Table S2). Gram-negative bacilli (*Escherichia coli*, *Klebsiella*, *Enterobacter* and *Pseudomonas aeruginosa*) contribute to < 10% of the cases. *Haemophilus influenzae* meningitis caused by the capsular b strains (Hib) was the leading cause of meningitis in infants and younger children but has become rare after universal Hib immunization with an emergening trend of H. Influenzae meningitis caused by uncapsulated strains. In immunocompromised patients, the most common agents causing ABM are *S. pneumoniae*, *L. monocytogenes* and Gram-negative bacilli, including

Ps. aeruginosa. Mixed bacterial infection with more than one agent typically accounts for 1% of all cases of ABM and is seen in patients who are immunosuppressed, have skull fracture or externally communicating dural fistula, parameningeal source of infection (otitis and sinusitis) and previous neurosurgery. Nosocomial bacterial meningitis is often caused by staphylococci (aureus and albus, including methicillin-resistant strains) and Gram-negative bacilli. Enterobacteriaceae are the most common aetiological agent of bacterial meningitis after neurosurgical procedures. The present guideline will not address the treatment of nosocomial meningitis and neonatal meningitis.

Presently, *S. pneumoniae* has emerged as the single most common cause of community-acquired bacterial meningitis after post-natal life both in the developed and developing countries [w5,w6]. *S. pneumoniae* is susceptible to penicillins and cephalosporins although emergence of penicillin and cephalosporin-resistant *S. pneumoniae* has increased in the recent years [w7,w8,w9]. However, in children as well as in adults, the severity of disease and the outcome of meningitis caused by penicillin-sensitive *S. pneumoniae* are similar to those caused by the penicillin-resistant strains [w10,w11].

Early management of ABM

Early diagnosis and effective antibiotic treatment remains the cornerstone of successful management of ABM. An understanding of the pathophysiological 'time-table' of ABM [2], as summarized in Panel 1, is essential for its successful and timely management.

Clinical feaures of ABM

The suspicion of ABM is critically dependent on the early recognition of the meningitis syndrome. In a Dutch study of adults presenting with community-acquired ABM, the sensitivity of the classic triad of fever, neck stiffness and

Panel 1 Time line of ABM [2]

Early events			Intermediate events	Late events
Pathophysiology				
Phase 1	Phase 2	Phase 3		
Release of pro-inflammatory cytokines from bacterial invasion and consequent inflammation of subarachnoid space	Subpial encephalopathy induced by cytokines and other chemical Mediators	Breakdown in the blood-brain-barrier, transendothelial emigration of leukocytes and development of cerebral oedema	Impaired CBF, rising intracranial pressure and vasculitis	Focal neuronal injury
Clincal				
Fever, headache	Meningism, confusion, reduced CSF glucose	Impaired consciousness, elevated CSF pressure, increased CSF protein, focal symptoms	Obtundation, seizures, focal neurological symptoms and/signs (e.g. cranial nerve palsies)	Paralysis, cognitive impairment coma, possibly death in untreated cases

Other infective meningitis and meningoencephalitis
(viral, tuberculous, fungal, leptospiral and primary amoebic)
Viral encephalitis
Brain abscess
Spinal epidural abscess (cervical)
Parameningeal infection (cranial osteomyelitis, subdural empyema)
Aseptic meningitis (e.g. SLE, Behcet's, sarcoidosis)
Chemical meningitis (e.g. after human IVIg therapy,
subarachnoid haemorrhage)

altered mental status was found to be low, but almost all patients with ABM had at least two of the four symptoms of headache, fever, neck stiffness and altered mental status [3]. In children, irritability, refusal to eat, vomiting and seizures are often early symptoms. The level of consciousness in ABM is variable and may range from drowsiness, confusion, stupor to coma.

Differential diagnosis

A high index of suspicion is required for the diagnosis of ABM and a list of common differential diagnosis is provided in Panel 2.

Initial management

Examination of CSF by LP is an undisputable and indispensible part of assessment of patients who present with symptoms and signs of meningitis unless the procedure is contraindicated by reasons of clinical safety. Clearly, treatment in ABM will be initiated in the hospital setting for the majority of cases, and after the diagnosis of bacterial meningitis is confirmed by the CSF formula obtained by LP. However, there will be situations where the antibiotic treatment may have to be commenced on suspicion before it is possible to confirm the diagnosis of ABM by CSF examination. This could happen in a primary care setting where transfer to a secondary care unit is probably to take some time. Even in hospitalized patients, CSF analysis may have to be delayed because of clinical or logistic reasons.

There are no randomized controlled trials to determine the outcome of bacterial meningitis based on timing of administration of the antibiotic. There are no prospective case–control studies of the potential benefit of pre-hospital antibiotic treatment. The evidence is conflicting between countries and pooled analysis of all the published results did not confirm the perceived advantage of pre-hospital antibiotic treatment in ABM which may relate to differences in sample size and reporting bias [w11]. In a case–control study of 158 children (age group 0–16 years) with suspected meningococcal disease, pre-hospital treatment by general practitioners with parenteral penicillin was associated with an increased odds ratios for death [7.4, 95% confidence interval (CI) 1.5–37.7] and complications in survivors (5.0, CI 1.7–15.0) [4]. The adverse outcome from pre-hospital antibiotic therapy was interpreted as indicative of more severe disease in these cases and lack of supportive treatment before hospital admission. A recent multivariate regression analysis of a retrospective case study of 119 adults with ABM showed that time from presentation to antibiotic administration of >6 h was associated with an adjusted 8.4 times increased risk of death (95% CI 1.7–40.9) [5]. Absence of the classical triad of meningitis and delay in the diagnosis–treatment sequence (transfer to institution, CT scan before LP, antibiotics) were factors which were associated with the door-antibiotic time >6 h in this study. Delay in antibiotic administration beyond 3 h and penicillin-resistance were two major risk factors associated with adverse outcome in adults with severe pneumococcal meningitis [w12]. Despite relative paucity of controlled studies on the timing of antibiotics administration to the outcome of ABM, available data do point to a cut-off period of 3–6 h beyond which there is a significant increase in mortality.

In patients visiting to the hospital, empirical antibiotic treatment for ABM should be considered before CSF analysis only if LP is contraindicated (Panel 3), or the facility for rapid brain imaging (CT scan) prior to LP is not immediately available. A normal CT scan in a patient with clinical manifestations of cerebral herniation does not guarantee absence of risk from the procedure of LP [w13,w14,w15,w16]. In all cases of ABM,

Absolute (lumbar puncture is not to be recommended)
Signs of raised intracranial pressure
(papilloedema, decrebrate posturing)
Local skin infection in needle track
Evidence of obstructive hydrocephalus, cerebral oedema
or herniation in CT (or MR) scan of brain
Relative (appropriate therapeutic measures and/or investigations
are indicated before lumbar puncture)
Sepsis or hypotension (systolic blood pressure <100 mmHg,
diastolic blood pressure <60 mmHg): patients should be
stabilized first
Coagulation disorder (disseminated intravascular coagulopathy,
platelet count <50 000/mm^3, therapeutic use of warfarin):
appropriate correction first
Presence of focal neurological deficit, especially when
posterior fossa lesion is suspected[a]
Glasgow coma score of 8 or less[a]
Epileptic seizures[a]

[a]In all these cases, CT (or MR) scan of brain should be the first step. Isolated single cranial nerve palsy without papilloedema does not necessarily contraindicate LP without brain imaging.

blood cultures must be obtained first before any treatment is administered. The time taken for antibiotic therapy ideally should coincide with or occur immediately before the administration of adjunctive dexamethasone therapy for suspected pneumococcal and *H. influenzae* meningitis. The choice of empirical antibiotic in ABM may be influenced by a number of factors, including patient's age, systemic symptoms and local pattern of bacterial resistance. A recent Cochrane Database review however, found no clinically important difference between the third-generation cephalosporins (ceftriaxone or cefotaxime) and conventional antibiotics (penicillin or ampicillin–chloramphenicol or chloramphenicol) as the empirical therapy in the treatment of ABM [6].

Recommendation

- The Task Force recommends (Flow chart) that all patients with suspected ABM should be hospitalized as soon as possible [III A]. Care of patients with suspected ABM should be considered as an emergency and fast-tracked for rapid assessment and treatment. We propose the following timeline for management of ABM: admission to hospital within first 90 min of making contact with health service; and assessment and treatment commenced within 60 min of hospital admission, and no longer than 3 h after contact with health service [IVC].

- Pre-hospital antibiotic treatment should only be initiated for patients with strong suspicion of disseminated meningococcal infection (meningococcemia) because of the unpredictable risk of early circulatory collapse from adrenocortical necrosis (Waterhouse–Fredrichsen syndrome). For other patients, rapid pre-admission antibiotic therapy should be considered only if a delay in excess of 90 min in hospital transfer is anticipated [IIIC].

- LP and CSF analysis is the specific investigation required for diagnosis and management of ABM. Therefore, if diagnosis of bacterial meningitis is suspected and there are no clinical contraindications, LP should be performed as soon as safely possible [IIIC].

- In patients with symptoms and signs suggestive of raised intracranial pressure or with high risk of cerebral herniations following LP (imaging evidence of intracranial mass lesion, obstructive hydrocephalus or midline shift), diagnostic LP should be postponed [IA].

- In a patient with suspected ABM in whom LP is being delayed or postponed, antibiotic therapy should be commenced immediately after collecting blood sample for culture. IV or IM Benzyl Penicillin, or IV Cefotaxime or Ceftriaxone should be administered as empirical therapy for ABM and may be commenced immediately [IIIA].

- In patients with known history of severe beta-lactam allergy, vancomycin should be administered as the alternative for pneumococcal meningitis and chloramphenicol for meningococcal meningitis [IVC].

- In regions with known or suspected penicillin-resistant strains of pneumococcus, high dose vancomycin should be used in combination with a third-generation cephalosporin [IVC].

- Patients with risk factors for Listerial meningitis (old age, immunosuppressed and/or signs of rhombencephalitis) should receive IV amoxicillin in addition to a third-generation cephalosporin as the empirical treatment of ABM initially [IVC].

- Dexamethasone in high doses may be appropriate as an adjunctive therapy and should be given shortly before or with the first dose of antibiotics (see Adjunctive therapy on ABM).

- All ABM patients should be managed as medical emergencies and when available, treated in neurological intensive care units.

Investigations in ABM

The primary purpose of investigations in ABM is to confirm the diagnosis and to identify the causal bacteria. The recommended specific laboratory tests for patients with suspected ABM are listed in Panel 4. In uncomplicated meningitis, plain CT and MR scans are often normal. Contrast scans may show abnormal enhancement of basal cisterns and subarachnoid space (involving convexity, falx, tentorium, base of the brain) because of the presence of inflammatory exudates [w17,w18,w19]; some MRI methods may have high sensitivity [w20].

An increased CSF-opening pressure, high number of polymorphonuclear leukocytes and raised protein concentration, together with decreased CSF:plasma ratio of glucose (< 0.3) are characteristic findings supportive of ABM (Panel 5). Listerial meningitis may have CSF findings identical to chronic tuberculous or fungal meningitis [w22,w23,w24,w25].

The identification of the causal bacteria depends on staining (Table S3) and culture of CSF, which should always be tested in freshly obtained samples. Gram stain is used most widely and has the best predictive value, but it is probably less sensitive.

Identification of bacteria in CSF staining depends both on the bacterial concentration and the specific organism [w30]. The percentage of positive cultures (sensitivity) is variable and ranges between 50 and 90% for ABM [w23,w24,w31]. A variable percentage of 'positive' cultures are because of contaminanting
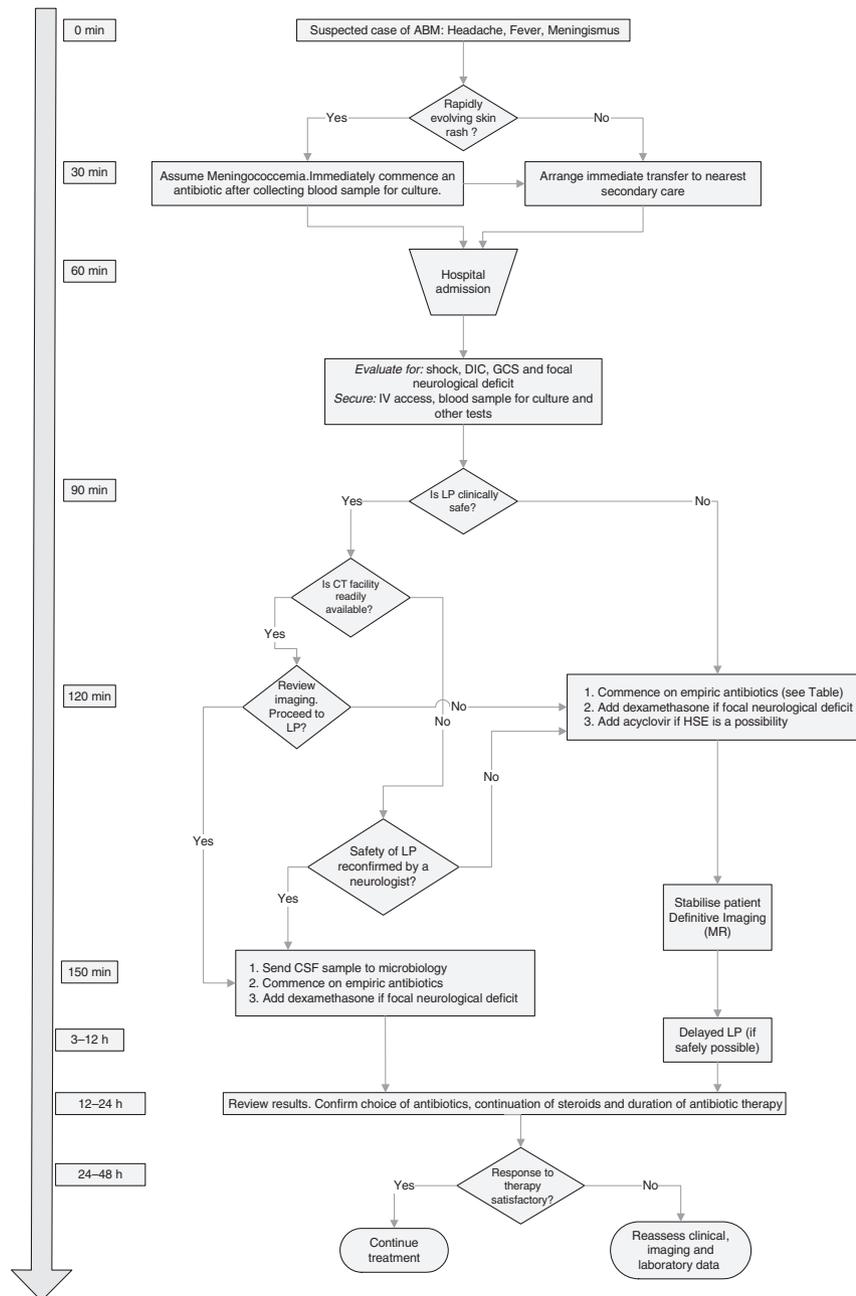
Flow chart Flow chart of emergency management of patients with suspected bacterial meningitis. ABM, acute bacterial meningitis; DIC, disseminated intravascular coagulation; GCS, Glasgow Coma Scale; HSE, herpes simplex encephalitis; LP, lumbar puncture.

organisms but not responsible for the meningeal infection [w31]. In patients with ABM, the probability of a negative CSF culture in previously treated patients is increased compared with non-treated patients (odds ratio 16; 95% CI 1.45–764.68; $P = 0.01$) [w32]. In ABM, the likelihood of diagnostic yield in CSF microbiology is highest before antibiotic treatment. Three other helpful and indirect diagnostic markers of ABM are: (a) elevated serum C-reactive protein (quantified) in children [w33] (sensitivity: 96%, specificity: 93%, nega-

tive predictive value: 99%); (b) increased CSF lactate [w34,w35] (sensitivity: 86–90%, specificity: 55–98%, positive predictive value: 19–96%, negative predictive value: 94–98%); and (c) high CSF ferritin [w36,w37,w38] (sensitivity: 92–96%,specificity: 81–100%).

Several rapid methods for detecting components of bacteria in CSF have been based on bacterial antigen detection, counterimmunoelectrophoresis, coagglutination, latex agglutination and ELISA. The average efficacy of these tests have been: sensitivity: 60–90%,

Panel 4 Laboratory investigations in acute bacterial meningitis (ABM)

Blood : (The 3 'C's)
  Culture
  Cell count
  C-reactive protein (CRP)
Cerebrospinal fluid (CSF)
  Opening pressure (always raised in ABM)
  Appearance
Cell count
  Biochemistry:
    Glucose, and the ratio of blood glucose
      (obtained before lumbar puncture)
    Protein
    Optional:lactate, ferritin, chloride, lactate dehydrogenase (LDH)
Microbiology:
  Gram stain, culture
  Others: counterimmunoelectrophoresis (CIE), radioimmunoassay
    (RIA), latex particle agglutination (LPA), enzyme-linked
    immunosorbent assay (ELISA), polymerase chain reaction (PCR)
Body fluid culture
  Petechial fluid, sputum, secretions from oropharynx, nose and ear

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specificity: 90–100%, predictive positive value: 60–85%, predictive negative value: 80–95% [w39, w40,w41,w42,w43]. Currently available PCR methods have a sensitivity of 87–100%, and specificity of 98–100% [w44,w45,w46,w47,w48], and detect *H. influenzae*, *N. meningitidis*, *S. pneumoniae*, *L. monocytogenes* in CSF. Fluorescence *in situ* hybridization (FISH) is less sensitive but may be useful for identification of bacteria in CSF samples in some cases [w49].

The CSF analysis may have to be repeated during the course of ABM in certain situations: partially treated cases, uncertain diagnosis, poor clinical response in the absence of other causes, vancomycin-treated patients receiving dexamethasone, Gram-negative bacillary meningitis, meningitis complicating CSF shunt and for intrathecal antibiotic therapy.

Specific antibiotic treatment

Clinical outcome in bacterial meningitis is directly related to concentrations of bacteria and bacterial antigens in the CSF [w50,w51]. Within the first 48 h of appropriate antibiotic therapy, CSF cultures invariably become sterile in pyogenic meningitis [w51]. In children with ABM, CSF sterilization of meningococci occurs within 2 h and pneumococci by 4 h. Third-generation cephalosporins are widely regarded as the standard of care in the empiric management of bacterial meningitis in both adults and children [w52,w53,w54,w55]. Ceftriaxone or cefotaxime have been compared with meropenem in licencing studies which were randomized but not controlled in adults and children and efficacy was found to be similar [w55].

Choice of treatment

Third-generation cephalosporins are the established empiric agents of choice in Europe and North America for Pneumococcal meningitis [w52,w53,w54]. When penicillin or cephalosporin resistance is possible then vancomycin should be combined with a third-generation cephalosporin. The combination has not been evaluated in randomized trials. Although there have been concerns regarding the penetration of vancomycin across the blood–brain barrier, when corticosteroids are used, a prospective study of 14 patients treated with vancomycin, ceftriaxone and dexamethasone confirmed therapeutic CSF concentration of vancomycin (7.2 mg/l; corresponding serum concentration 25.2 mg/l) at 72 h [7]. Rifampicin penetrates blood–brain barrier well and an animal model reduces early mortality in pneumococcal meningitis [w56]. It therefore should be considered in addition to vancomycin. If confirmed or strongly suspected (presence of the typical rash), meningococcal

Panel 5 Comparison of cerebrospinal fluid findings (CSF) of meningitis

	Acute bacterial meningitis	Viral meningitis/ meningo-encephalitis	Chronic meningitis (tuberculous meningitis)	Normal CSF
Characteristics	Turbid, cloudy, purulent	Clear	Clear, cloudy	Clear
Opening pressure (mm H_2O)	>180	>180	>180	180 (upper limit)[a]
WBC count (cells/mm^3)	1000–10 000	5–1000	25–500[b]	0–5 (0–30 in newborns)
Neutrophils (%)	>60[c]	<20	<50[c]	0–15
Protein (g/l)	>0.5	<1.0	>0.5	0.15–0.5
Glucose (mM)	<2.5	2.5–4.5	<2.5	2.5–4.5
CSF/blood glucose ratio	<0.3	>0.5	<0.5	0.6

[a]It may reach 250 mm H_2O in obese adults [w21].
[b]Higher cellularity in tuberculous meningitis has been occasionally observed in immunocompetent and BCG-vaccinated subjects soon after the initiation of anti-tuberculous therapy.
[c]Neutrophilic response in tuberculous meningitis is known with acute onset and in HIV patients. Lymphocytic pleocytosis in ABM is seen in cases who have already been partially treated with antibiotics.
ABM, acute bacterial meningitis.

meningitis should be treated with benzyl penicillin or a third-generation cephalosporin, or chloramphenicol if there is a history of life-threatening beta-lactam allergy. Listeria is intrinsically resistant to the cephalosporins and suspected listerial meningitis should be treated with high dose IV ampicillin or amoxicillin usually in conjunction with IV gentamicin (1–2 mg/kg 8 h) for the first 7–10 days which is synergistic *in vivo*, or with high dose IV cotrimoxazole when there is history of penicillin allergy [w52,w54,w57]. The doses for common antibiotics in children are provided in Table S4.

There are no randomized controlled trials on the treatment of staphylococcal meningitis which is usually nosocomial (e.g. shunt infection). Linezolid has been used in a number of case reports with good success and pharmacokinetics are persuasive and may be an option for the treatment of methicillin-resistant staphylococcal meningitis and ventriculitis [w58]. Lizezolid however requires to be used with caution, because of adverse events and drug interactions, particularly in the intensive care when vasoactive agents are used. The use of intrathecal or intraventricular antibiotics is to be considered in patients who fail conventional treatment. Intraventricular vancomycin may achieve better CSF concentration as compared with intravenous route and the addition of intrathecal or intrventricular aminoglycosides as an additional agent is an option for patients with Gram-negative bacillary meningitis who do not respond well to monotherapy.

Recommendation

- Initial antibiotic treatment of ABM should be parenteral [IA].

Empirical antibiotic therapy in suspected ABM

Ceftriaxone 2 g 12–24 hourly or Cefotaxime 2 g 6–8 hourly [IIIB]
Alternative therapy; Meropenem 2 g 8 hourly [IIIC] or Chloramphenicol 1 g 6 hourly.
If penicillin or cephalosporin-resistant pneumococcus is suspected, use Ceftriaxone or Cefotaxime plus Vancomycin 60 mg/kg/24 hourly (adjusted for creatinine clearance) after loading dose of 15 mg/kg [IVA].
Ampicillin/Amoxicillin 2 g 4 hourly if *Listeria* is suspected [IVA].

Pathogen specific therapy

i. Penicillin-sensitive Pneumococcal meningitis (and including other sensitive Streptococcal species);
   Benzyl Penicillin 250 000 U/kg/day (equivalent to 2.4 g 4 hourly) [IVA] or Ampicillin/Amoxicillin 2 g

4 hourly or Ceftriaxone 2 g 12 hourly or Cefotaxime 2 g 6–8 hourly.
   Alternative therapy; Meropenem 2 g 8 hourly [IVC] or Vancomycin 60 mg/kg/24 hourly as continuous infusión (adjusted for creatinine clearance) after 15 mg/kg loading dose aiming for serum levels of 15–25 mg/l) plus Rifampicin 600 mg 12 hourly [IVC] or,
   Moxifloxacin 400 mg daily [IVC]
ii. Pneumococcus with reduced susceptibility to penicillin or cephalosporins;
   Ceftriaxone or Cefotaxime plus Vancomycin ± Rifampicin [IV]. Alternative therapy Moxifloxacin, Meropenem or Linezolid 600 mg combined with Rifampicin [IV]
iii. Menigococcal meningitis
   Benzyl Penicillin or Ceftriaxone or Cefotaxime [IV]
   Alternative therapy; Meropenem or Chloramphenicol or Moxifloxacin [IVC]
iv. Haemophilus infuenzae type B
   Ceftriaxone or Cefotaxime [IVC]
   Alternative therapy; IV Chloramphenicol–Ampicillin/Amoxicillin [IVC]
v. Listerial meningitis
   Ampicillin or Amoxicillin 2 g 4 hourly
   ± Gentamicin 1–2 mg 8 hourly for the first 7–10 days [IVC]
   Alternative therapy, Trimethoprim–Sulfamethoxazole 10–20 mg/kg 6–12 hourly or Meropenem [IV]
vi. Staphylococcal species; Flucloxacillin 2 g 4 hourly [IV] or
   Vancomycin if penicillin allergy is suspected [IV]. Rifampicin should also be considered in addition to either agent, and Linezolid for methicillin-resistant staphylococcal meningitis [IVC].
vii. Gram-negative Enterobacteriaceae
   Ceftriaxone or Cefotaxime or Meropenem
viii. Pseudomonal meningitis
   Meropenem ± Gentamicin

Duration of therapy

The optimum duration of therapy in ABM is not known. In a prospective, observational study of meningococcal disease in adults from New Zealand, which had a majority of cases with meningitis, a 3-day course of IV benzyl penicillin was successful [w59]. Amongst children with uncomplicated ABM, 7 days of ceftriaxone was found to be equivalent to 10 days in India [w60] and 4 days was found to be equivalent to 7 days in Chile [w61]. In a Swiss multicentre study in children short course therapy (7 days or less) was equivalent to 8–12 days of treatment with ceftriaxone [w62]. Two single doses of intramuscular

oily chloramphenicol separated by 48 h were found in African children to be equivalent to 8 days parenteral ampicillin [w63]. In the absence of controlled clinical trials in adults, the recommended duration of antibiotic therapy in ABM is based on current standards of practice and in most cases with early and uncomplicated ABM, the shorter range of therapy would be appropriate.

Recommendation

- Unspecified bacterial meningitis 10–14 days [IVC].
- Pneumococcal meningitis 10–14 days [IVA].
- Meningococcal meningitis 5–7 days [IVA].
- Hib meningitis 7–14 days [IVB].
- Listerial meningitis 21 days [IVB].
- Gram-negative bacillary and Pseudomonal meningitis: 21–28 days [IVB].

Monitoring treatment

In general, if clinical condition does not improve by 48 h after commencing appropriate antibiotics (and dexamethasone when indicated), the following considerations should be given:

- raised intracranial pressure from cerebral oedema or obstructive hydrocephalus
- vascular complications (arteritis or venous sinus thrombosis)
- inappropriate antibiotic
- poor antibiotic penetration (e.g. vancomycin if patient on dexamethasone)
- wrong diagnosis
- epileptic seizures (e.g. non-convulsive status)
- metabolic complications (e.g. SIADH)
- persistence of source of primary infection (e.g. pneumonia, bacterial endocarditis, mastoiditis or otitis)

Risk scores for unfavourable outcome in ABM have been recently validated both in adults [8] and children [9] and may be useful as prognostic tools. In a retrospective study, disturbed level of consciousness and higher age at the time of admission were found to be risk factors for developing hydrocephalus in the early phase of ABM [w64]. CT or MR scans of brain can identify areas of ischaemia or infarction, brain abscess. subdural empyema, signs of venous sinus thrombosis, hydrocephalus and ventriculitis [IIIB].

Adjunctive therapy of ABM

Corticosteroids

Of all the adjunctive treatments in ABM, only corticosteroids have been properly evaluated in clinical trials. The rationale for using corticosteroids was that the treatment would attenuate subarachnoid space inflammation and vasogenic oedema in meningitis that may have potentially serious and damaging effects [2]. In 1988, published results of two-double blind, placebo-controlled trials of dexamethasone as adjunctive treatment of bacterial meningitis in infants and older children showed convincing benefit from steroid therapy (decreased incidence of sensorineural hearing loss in the treated children with Hib meningitis) [w65]. In two subsequent trials in paediatric patients, dexamethasone given before or with the first dose of antibiotic significantly reduced one or more neurological sequelae [w66,w67]. In 1997, a meta-analysis of all randomized clinical trials since 1988 using dexamethasone as adjunctive therapy in bacterial meningitis concluded that steroid treatment benefited Hib meningitis and when commenced with or before parenteral antibiotics, showed benefit for children with pneumococcal meningitis [w68].

A large prospective, open trial of dexamethasone in adults showed a benefit of dexamethasone therapy in a subgroup of patients with pneumococcal meningitis [w69]. Another multi-centre double blind, randomized trial of dexamethasone treatment for severe bacterial meningitis in adults proved inconclusive because the trial was stopped prematurely because of the emergence of penicillin-resistant *S. pneumoniae* [w70]. A placebo-controlled double blind trial of dexamethasone in 40 adult patients from India concluded that the steroid treatment reduced neurological complications because of meningitis but secondary fever, gastrointestinal manifestations and neuropsychiatric symptoms were common side effects in the treated group [w71].

Results of a double blind, placebo-controlled, randomized European trial of dexamethasone in 301 adult patients with ABM in adults showed that early steroid use (before or with first dose of antibiotics) is associated with an improved survival and significantly better outcome in these patients as measured by the Glasgow Outcome Scale at 8 weeks [10]. The benefit was by far most convincing in patients with pneumococcal meningitis who were given dexamethasone (10 mg 6 hourly for first 4 days) beginning before or with the first dose of the antibiotic. The benefit of adjuvant dexamethasone in this trial was not undermined by any increase in the incidence of severe neurological disability in patients who survived, or by any serious steroid-induced complications.

The positive outcome of the European dexamethasone trial in adult bacterial meningitis contrasted sharply with the results of a randomized controlled trial of adjuvant dexamethasone in 598 children with bacterial meningitis from Malawi [w72]. The Malawi trial failed to demonstrate any treatment benefit in terms of survival or neurological outcome. A recently published

trial of dexamethasone in adult patients with bacterial meningitis from Malawi [w73] reached very similar conclusions. In this trial, mortality was exceptionally high in both groups of patients receiving dexamethasone (56% of 233 patients) or placebo (53% of 232 patients) at 40 days and there was also no difference in disability rates or hearing loss between these groups at 6 months. Nearly 90% patients in this study were seropositive for HIV infection. The results of the Vietnamese trial of dexamethasone in bacterial meningitis [w74], was however more favourable for the steroid-treated patients with proven ABM. In this trial, 435 subjects older than 14 years were randomly assigned to receive 0.4 mg/kg of dexamethasone ($n = 217$) or placebo ($n = 218$) every 12 h for 4 days commencing shortly before the administration of antibiotics in most cases with meningitis caused by S. suis (which is similar to S. pneumoniae).

Taken together, results of these trials confirm the earlier view [2] that longer use (for 4 days) of dexamethasone in pharmacological doses is not appropriate if patients are probably to be immunocompromised or have a tentaive diagnosis of ABM unsupported by appropriate investigations. The role of dexamethasone as an adjunctive therapy in ABM is clearly maximal in those who are not significantly immunosuppressed and have a confirmed microbiological diagnosis of ABM. In the context of the bacterial aetiology of ABM, evidence confirms its therapeutic benefit in cases with pneumococcal and Hib meningitis. Wider use of high dose dexamethasone in ABM because of other bacterial aetiologies is currently proposed [w75,w76], but its therapeutic benefit is not conclusive across all groups of patients.

Recommendation

- Adjuvant dexamethasone is recommended with or shortly before the first parenteral dose of antibiotic in all previously well and non-immunosuppressed adults with pneumococcal meningitis at a dose of 10 mg every 6 h for 4 days [IA] and children at a dose of 0.15 mg/kg every 6 h for 4 days for Hib and pneumococcal meningitis [IA].
- In all patients with clinically suspected pneumococcal (or Hib) meningitis (early focal neurological signs), we recommend that dexamethasone is given with the first dose of empirical antibiotic therapy as above [IVC].
- In ABM because of other bacterial aetiology, routine use of high dose dexamethasone is not presently recommended [IA].
- If dexamethasone was initiated on clinical suspicion of ABM, which was subsequently proven to be inaccurate by CSF microbiolgy, the treatment should be promptly withdrawn.

- There is insufficient evidence to recommend the use of dexamethasone in pharmacological doses after antibiotic therapy has begun. Dose and duration of therapy with corticosteroids in such cases should be guided by specific clinical indications in individual patients (e.g. physiological doses of steroids in cases of adrenal insufficiency because of meningococcemia, pharmacological doses of steroids for raised intracranial pressure).
- By reducing subarachnoid space inflammation and blood brain barrier permeability, steroids may lower CSF penetration of antibiotics and patients receiving vancomycin for penicillin-resistant pneumococcal meningitis require close clinical and CSF monitoring.

Other symptomatic and adjunctive therapies

Circulatory shock as part of severe sepsis or in meningococcemia should be handled in neurointensive care unit. Treatment should consist of a 30° head-up position, head midline, minimal suction, deep sedation, normo- or moderate hypothermia and strict avoidance of hypercapnia [11]. Head elevation and hyperosmolar agents are recommended for the management of cerebral oedema but have never been systematically evaluated in the context of bacterial meningitis. As a hyperosmolar agent, 20% mannitol may be given intravenously either as a bolus injection of 1 g/kg over 10–15 min, repeated at 4–6 h intervals, or in smaller but frequent doses (0.25 mg/kg every 2–3 h), to maintain a target serum osmolality of 315–320 mOsm/l [IVC]. CSF pressure monitoring may be helpful in cases where CSF drainage (ventricular) is under consideration for obstructive hydrocephalus, and the decision to perform the procedure should be based on patient's level of consciousness and the degree of ventricular dilatation visualized in brain imaging (CT or MRI) [IVC]. Seizures are frequent in ABM and are associated with severe inflammation, structural brain lesion and pneumococcal meningitis, may increase mortality [12] and should be treated with a parenteral anticonvulsant, such as phenytoin (fosphenytoin) [IIIB]. Prophylactic anticoagulation to prevent deep vein thrombosis may be considered in patients who do not have coagulaopathy and are considered to be at a high risk of deep vein thrombosis (e.g. obesity and recent hip surgery). Heparin was considered beneficial in a retrospective study of patients with septic cavernous sinus thrombosis [w77]; however, experience with therapeutic anticoagulation for venous sinus thrombosis in ABM is limited and is best reserved for patients who deteriorate neurologically because of venous sinus thrombosis and require close monitoring of coagulation profile and brain imaging [IVC].

Managing complications of ABM

Death in bacterial meningitis may occur within the first 48 h and sometimes even before the diagnosis could be suspected. In a review of the autopsy data, it was noted that deaths because of *N. meningitidis* often occurred within 12–24 h of the first symptoms [w78]. Delayed neurological sequelae may occur in 20–40% of patients. Audiological complications have been reported in over a third of children with bacterial meningitis, mostly because of *H. influenzae*. Cognitive dysfunction, behavioural changes, seizures and motor impairment are common complications of meningitis both in adults and in children. Some survivors have permanent visual impairment, caused by optic atrophy from opticochiasmatic arachnoiditis, persistent hydrocephalus or as a result of cortical blindness from arterial infarction involving the occipital lobes. The range of post-meningitic motor deficits include unilateral or bilateral hemiparesis, weakness of eye movements, spastic paraparesis with sensory loss from spinal cord damage and rarely, a tabetic syndrome because of the involvement of lumbosacral nerve roots. Growth retardation and arrest of mental development are delayed complications of bacterial meningitis seen in children. The range of complications in pneumococcal meningitis is particularly severe. Austrian sydrome is a severe condition of invasive pneumococcal disease characterized by meningitis, endocarditis and pneumonia which carries a high rate of mortality. A recent study in adults has drawn attention to problems such as myelitis and subarachnoid bleeding and higher incidences of cerebrovascular lesions (22% arterial and 9% venous strokes) [13]. Chronic fatigue, depression and sleep disorders are significantly higher amongst the survivors of meningitis and a smaller proportion of patients may present with epilepsy in later years (Table S5).

Recommendation

- All survivors of ABM should be offered access to neurology service.
- Audiometry is recommended in recovering patients with suspected hearing impairment.
- Seizures in patients with ABM may be early (acute symptomatic epilepsy) or delayed, appearing after several months or years. Long-term antiepileptic drug therapy is recommended in patients with late-onset seizures. For patients with acute symptomatic seizures, antiepileptic drug therapy may be withdrawn after 1 year, in the absence of seizure recurrence and structural brain (cortical) injury as visualized in brain imaging.
- Driving restriction in adults may apply if they had seizures, or have functional impairment such as visual field defect and limb weakness.

Prevention of secondary cases of ABM

It is the responsibility of the diagnosing clinician to inform the local public health authorities of any case of suspected invasive meningococcal infection. Asymptomatic carriers of *N. meningitidis* may pass the organism via droplet/close contact spread to others, usually a household member or a close 'kissing' contact, who, in turn may become a carrier or may develop invasive infection. Secondary cases in close contacts occur at a rate of about 2–4/1000 [w79]. Asymptomatic carriers are the target of chemoprophylaxis. A meta-analysis of retrospective, uncontrolled, observational studies of chemoprophylaxis with either rifampicin, minocycline, sulphonamide or ciprofloxacin versus no chemoprophylaxis demonstrated an 89% reduction in risk in secondary house-hold cases with about 200 contacts needed to be treated to prevent one further case [w80]. In Nordic countries, antibiotic therapy with 7 days of oral penicillin is also recommended, in addition to chemoprophylaxis, for household contacts under the age of 15 years to treat early or incubating infection which may be unaffected by chemoprophylaxis alone [w81]. As benzyl penicillin does not eradicate carriage, all patients with meningococcal infection who have not received a third generation cephalosporin should receive further antibiotic prophylaxis with either rifampicin for 2 days or with a single dose of ciprofloxacin or ceftriaxone. If vaccine preventable strains are implicated (serotypes A or C) in the outbreak setting, vaccination should be given to all unvaccinated household or close contacts. Patients at risk of primary meningococcal infection, including travellers to endemic areas, the immunosuppressed and the aspleenic should be offered primary immunization. The polysaccharide–protein conjugated meningococcal type C vaccine is highly effective at preventing serotype C infections and is part of the standard childhood immunization schedule in much of Europe [w82].

Primary prevention of pneumococcal disease in general with the pneumococcal vaccine should be offered to all immunosuppressed and aspleenic patients and to those with chronic pulmonary, renal, hepatic or cardiac disease or those aged over 65 years, those with a cochlear implant, previous basal skull fracture, *in situ* CSF shunt or CSF leak. Aspleenic or hypospleenic individuals (e.g. those with sickle cell disease) are also at risk of invasive disease. In at risk individuals, vaccination may be repeated at five yearly intervals. Although Hib very rarely causes meningitis in adults, if this does

occur, all household members should have their vaccination status evaluated. Prophylaxis with rifampicin is recommended and unimmunized children should be vaccinated against Hib.

Recommendation

- All cases of suspected meningococcal or Hib meningitis should be reported urgently to the local public health authorities [IVC].
- Chemoprophylaxis with either oral rifampicin (600 mg 12 hourly for 48 h), ciprofloxacin (500 mg single dose) or ceftriaxone (IV or IM injection of a single 1 g dose) should be given to those adults with meningococcal infection who were treated without a third-generation cephalosporin [IVC].
- Chemoprophylaxis with either Rifampicin, Ciprofloxacin or Ceftriaxone should be given to household or close contacts of patients with suspected or proven meningococcal or Haemophilus infection [IVC].
- A therapeutic 7-day course of Phenoxymethyl Penicillin or Amoxicillin should be considered in addition to chemoprophylaxis for any household or close contact of a patient with meningococcal disease aged < 15 years [IVC].
- Chemoprophylaxis for meningococcal meningitis is rarely indicated for health-care workers and is only recommended in situations where there has been mouth to mouth contact or direct exposure to infectious droplets from a patient with meningococcal disease [IVC].
- Immunization with Meningococcal or *H. influenzae* type B vaccine should be considered in the public health management of an outbreak [IVC].
- Primary vaccination against *N. meningitidis* and *H. influenzae* type B infection should be given to all at risk groups [IVC].
- Vaccination against *N. meningitides* type C and *H. influenzae* type B should be given to all children as part of the normal childhood immunization schedule [IVC].

Supplementary material

The full (unabridged) version of this article is available as supplementary material as part of the online article from: http://www.blackwell-synergy.com/doi/abs/10.1111/j.1468-1331.2008.02193.x
(This link will take you to the article abstract).

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