Journal of Infection (2016) 72, 405–438

BIA
British Infection Association

www.elsevierhealth.com/journals/jinf

The UK joint specialist societies guideline on the diagnosis and management of acute meningitis and meningococcal sepsis in immunocompetent adults☆

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http://dx.doi.org/10.1016/j.jinf.2016.01.007

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Accepted 23 January 2016
Available online 2 February 2016

KEYWORDS
Meningitis;
Meningococcal sepsis;
Adults;
Guideline

Summary Bacterial meningitis and meningococcal sepsis are rare conditions with high case fatality rates. Early recognition and prompt treatment saves lives. In 1999 the British Infection Society produced a consensus statement for the management of immunocompetent adults with meningitis and meningococcal sepsis.

Since 1999 there have been many changes. We therefore set out to produce revised guidelines which provide a standardised evidence-based approach to the management of acute community acquired meningitis and meningococcal sepsis in adults.

A working party consisting of infectious diseases physicians, neurologists, acute physicians, intensivists, microbiologists, public health experts and patient group representatives was formed. Key questions were identified and the literature reviewed. All recommendations were graded and agreed upon by the working party. The guidelines, which for the first time include viral meningitis, are written in accordance with the AGREE 2 tool and recommendations graded according to the GRADE system.

Main changes from the original statement include the indications for pre-hospital antibiotics, timing of the lumbar puncture and the indications for neuroimaging. The list of investigations has been updated and more emphasis is placed on molecular diagnosis. Approaches to both antibiotic and steroid therapy have been revised. Several recommendations have been given regarding the follow-up of patients.

Introduction

Although bacterial meningitis and meningococcal sepsis are rare in adults and the average UK NHS district general hospital will see ten or fewer laboratory confirmed cases per year, they continue to carry a high morbidity and mortality. Delays in diagnosis and treatment can have disastrous consequences so prompt recognition and treatment are essential. The British Infection Society (the predecessor of the British Infection Association) published a consensus statement on the management of meningitis and meningococcal sepsis in adults in 1999.[1]This was followed by a management algorithm in 2003, which was produced and distributed by the Meningitis Research Foundation.[2] Since then, the epidemiology has changed, especially following changes in immunisation programmes, and there are new diagnostics and further data available regarding adjunctive treatments. In addition, global increases in the prevalence of antibiotic resistant bacteria underlines the importance of good antimicrobial stewardship. The partner organisations for these updated guidelines formed a working party consisting of infectious diseases physicians, neurologists, acute physicians, intensivists, microbiologists, paediatricians, public health experts and patient group representatives to review the literature published since 1999 and update the recommendations in light of any new evidence. The working party included representatives of the original authors from the 1999 consensus statement. The working party aimed to create user-friendly, comprehensive guidelines primarily for hospital-based clinicians in the UK with auditable outcomes. In addition to the published manuscript there is also an updated algorithm to aid emergency management. Key changes are highlighted in Box 1. These guidelines may also be useful to clinicians from other countries or settings, although there are other international guidelines available (Box 2).

Definitions

Some definitions are given in Table 1.

Epidemiology

Estimates of the incidence of bacterial meningitis and meningococcal sepsis in the UK are derived from several

Box 1. Key Changes since consensus document in 1999.

- Updated epidemiology
- Change in recommendations regarding pre-hospital antibiotics
- Clear guidance on when to perform a CT scan
- Recommended durations of antibiotics and adjunctive treatment including the removal of activated protein C.
- Updated recommendations on empirical antibiotics
- Recommendations regarding outpatient treatment
- Updated guidance on prophylaxis for contacts
- Infection control advice
- The addition of a section on viral meningitis
- Audit tool

Box 2. Guidelines which may be of use in other settings.

- Infectious Diseases Society of America http://www.idsociety.org/uploadedFiles/IDSA/Guidelines-Patient_Care/PDF_Library/Bacterial%20Meningitis%281%29.pdf
- European Federation of Neurological Sciences http://www.eaneurology.org/Guideline-Archive-by-topic.1358.0.html
- European Society of Clinical Microbiology and Infectious Diseases Diagnosis and treatment of acute bacterial meningitis (in press Feb 2016)www.escmid.org/escmid_library/medical_guidelines/escmid_guidelines/
- Federation of Infectious Diseases Society of Southern Africa http://www.sajei.co.za/index.php/SAJEI/article/viewFile/528/686
- Ministry of Health, Social Services and Quality, Spain. http://www.guiasalud.es/GPC/GPC_525_EMI_ICS_compl_en.pdf

Table 1 Definitions.

Meningism	Symptoms of headache, neck stiffness and photophobia often associated with meningitis
Meningitis	Inflammation of the meninges Strictly a pathological diagnosis Elevated cerebrospinal fluid white cell count and protein are normally used as indicators of inflammation Meningeal enhancement may be seen on contrast enhanced CT or MRI
Sepsis	Presence of infection with systemic manifestations such as: • Fever or hypothermia • Tachycardia • Tachypnoea • Altered mental state (see the surviving sepsis guidelines for a full list of potential manifestations of sepsis[41])
Severe sepsis	Acute organ dysfunction secondary to documented or suspected sepsis
Septic shock	Severe sepsis plus hypotension not reversed with fluid resuscitation
Meningococcal sepsis	Evidence of sepsis with or without a characteristic petechial/purpuric skin rash and hypoperfusion. *Neisseria meningitidis* may be identified from blood, CSF or skin lesions (culture or PCR).
Invasive meningococcal disease (IMD)	Invasion of any normally sterile site by *Neisseria meningitidis* including meningitis and bacteraemia
Encephalitis	Inflammation of the brain parenchyma Strictly a pathological diagnosis Elevated cerebrospinal fluid white cell count and protein normally used to indicate inflammation Parenchymal inflammation may be seen on MRI
Meningoencephalitis	Inflammation of the meninges and adjoining brain parenchyma
Aseptic Meningitis	Symptoms of meningism and raised numbers of cells in the CSF with a sterile bacterial culture.

sources of information including clinical and laboratory statutory notifications, Hospital Episode Statistics and the Office of National Statistics. Although meningitis is a notifiable disease in the UK and in other countries, it is widely believed to be underreported.[3,4] Several studies have shown reductions in the frequency of bacterial meningitis and meningococcal sepsis in recent years, although these largely reflect changes seen in children. Disease in adults has remained stable or increased.[5,6] A recent study in England and Wales showed an increase in the incidence of meningitis in adults between 2004 and 2011, with an increase of 3% per year in patients over 65 years of age. The incidence in adults was estimated to be 1.05 cases per 100,000 population (between 2004 and 2011) with the highest incidence in the 45–64 age group (1.21 per 100,000).[7] The mortality rate of community acquired bacterial meningitis is high, approximately 20% for all causes and up to 30% in pneumococcal meningitis, increasing with age.[8,9]

The number of cases of invasive meningococcal disease (including meningitis and meningococcal sepsis) has declined over the last decade in the UK, following the introduction of the group C vaccine and the natural variation of meningococci. Meningococcal disease has a bimodal distribution with one peak in children less than 5 years of age and a second peak in the adolescent/early adult age group.[10–12] Amongst adults, the incidence of meningococcal disease is highest in younger adults, between the ages of 16–25.[7,13] Other bacteria that cause meningitis in adults include *Listeria monocytogenes* (most commonly in older adults and the immunocompromised), *Streptococcus pyogenes, Enterococcus* species, Group B streptococcus, non-type B *Haemophilus influenzae* and other gram negative bacteria such as *Klebsiella, Pseudomonas and Enterobacter.*[7] *Mycobacterium tuberculosis* should also be considered in those with appropriate risk factors, even in patients with an acute presentation.

The likelihood of any specific aetiology depends on a range of factors, see Table 2 for some key considerations and risk factors. In many cases (34%–74%), no pathogen is identified.[14–19]

Aims and scope of the guidelines

These guidelines cover the management of adults with suspected and confirmed acute meningitis and meningococcal sepsis, from pre-hospital care to post-discharge support, including clinical features, investigations, treatment, follow-up and prevention. As previously the guidelines focus on bacterial meningitis and meningococcal sepsis but now also include a section on viral meningitis which is increasing in relative importance. Meningitis in immunocompromised individuals, post-surgical/iatrogenic meningitis and tuberculous meningitis are beyond the scope of these guidelines and not considered further. Guidelines

Table 2 Key aetiological considerations for specific demographic groups.

Young adults	Viral meningitis more common than bacterial, especially in women in their 20s–40s. Second peak of meningococcal disease in late teens/early 20s
Older adults	Pneumococcal disease more common in over 50s *Listeria* commoner in over 60s but remains rare.
Skull fracture/CSF leak	Pneumococcal meningitis and a risk factor for recurrent meningitis
Previous lymphocytic meningitis	HSV-2 is the commonest cause of recurrent lymphocytic meningitis
Rash	Meningococcal meningitis more likely to present with a rash than pneumococcal meningitis
Co-existing upper respiratory tract infection e.g. otitis media, sinusitis	Pneumococcal meningitis is often associated with an upper respiratory tract infection
HIV Positive	Cryptococcal meningitis – commonest in those with a CD4 count $<100 \times 10^6$ but should be considered in anyone with a CD4 count of $<200 \times 10^6$ or <14%. TB meningitis an important consideration at all CD4 counts Pneumococcal meningitis also increased
Other immunocompromised	Asplenic individuals are at increased risk from all encapsulated bacteria e.g. *Streptococcus pneumoniae, Neisseria meningitidis* and *Haemophilus influenzae*. Complement deficiency increases risk of meningococcal disease. Risk factors for *listeria* meningitis include relative immunocompromise from alcohol dependency, diabetes and malignancy as well as overt immunocompromised from illness or medication.
Travel history	An appropriate travel history may determine other rarer causes including Toscana Virus (Mediterranean), Tick Borne Encephalitis Virus (Central and Eastern Europe), other meningococcal (meningitis belt in Africa), West Nile Virus (USA), Lyme disease (appropriate exposure in Europe or USA) and parasitic meningitis (such as *Naegleri fowleri* – abundant globally occurring following visits to warm, fresh or brackish water, or trypanosomiasis – South America or parts of Africa).

Box 3. Key questions.

- What are the indications for hospital admission?
- What should the pre-hospital management be?
- What are the clinical signs to look for including early recognition?
- What is the initial assessment and immediate action?
- Are prognostic or diagnostic scores of any value?
- What are the contraindication to LP?
- What are the indications for imaging?
- What investigations should be requested?
  - Microbiological
  - Biochemical
  - Haematological
  - Others (including travel related)
- When should an HIV test be offered?
- What treatment should be given?
  - Empirical
  - Directed
  - Adjunctive
- What is the role of steroids?
- What is the role of glycerol?
- When should you refer to specialists/intensive care?
- What is the role for fluid management, inotropes and indications for ventilation?
- What should the intensive care management be?
- What preventative measures should/can be taken? (including notification and primary and secondary prevention)
- What are the appropriate infection control measures?
- Who should be screened for predisposing factors?
- What should follow up look like? (including the role of support services)
- How should viral meningitis be investigated and treated?
- What are the auditable measures? (to include an audit tool)
- When should this guideline be reviewed?

on the management of tuberculous meningitis[20] and the management of bacterial meningitis and sepsis in children are available elsewhere.[21]

Methods

A literature search was performed in Medline for all English language articles from the years 1999—2014 to identify all publications since the first British Infection Society guidelines were published using the key words 'meningitis' AND 'symptoms'; 'signs'; 'management'; 'diagnosis'; 'investigation'; 'lumbar puncture'; 'cerebrospinal fluid'; 'computed tomography (CT)'; 'magnetic resonance imaging (MRI)'; 'treatment'; 'antiviral'; 'antibiotic'; 'steroids/dexamethasone'; 'prevention'; 'risk factors' and 'immunocompromise' separately and in combination with the following MESH terms: (Viral, meningococcal, pneumococcal, *Haemophilus*, bacterial). This yielded a total of 5027 citations. The working party identified the main questions that we wanted to address (see Box 3); titles and abstracts were reviewed by one author (FM) to eliminate articles that were not relevant to these questions. This left 621 articles which were then reviewed in full by 3 members of the writing group (BDM, FM, SD) to remove any further articles that were felt not to be helpful in answering the questions identified; mostly these were case reports or studies relevant to specific populations only. This resulted in 284 potentially relevant articles that were made available to the whole working party. All authors could also add to this core list of publications other articles, for example those published before 1999; this included many referenced in the original consensus statement.[1] A further literature search was done (by BDM and FM) prior to publication to identify any further relevant articles that had been published in the interim.

Using this final list of articles each section was written by a primary author and reviewed by others from the working party before being reviewed by the whole working party. When a final draft was agreed upon by the working party it was then sent for a first consultation to the boards and councils of all the partner organisations and then a second consultation to all the members of the partner organisations.

A single document was assimilated in accordance with the principles of the AGREE 2 (appraisal of guideline research and evaluation) tool,[22] and we used the GRADE approach to grade the strength of evidence (see Table 3).[23] Where recommendations are not based on published evidence but were agreed on by the working party, they are graded as "authors' recommendation" or "AR".

Presentation

Pre-hospital management

What are the indications for hospital admission and what are the clinical signs to look for?

Table 3 GRADE rating system for the strength of the guidelines recommendations and the quality of the evidence.[23]

Strength of the recommendation	Quality of the evidence
1 Strongly recommended **2** Weakly recommended	**A** High quality — RCT, meta-analysis **B** Moderate quality — downgraded RCT or an upgraded observational study
	C Low quality — Observational study **D** Very low quality — downgraded observational study.
a: Factors that may influence the grading of quality of evidence	
Factors that might decrease the quality of evidence	Factors that might increase the quality of evidence
Study Limitations Inconsistency of results Indirectness of evidence Imprecision Publication bias	Large magnitude of effect Plausible confounding, which would reduce a demonstrated effect Dose-response gradient
b. Factors that determine the strength of a recommendation	
Balance between desirable and undesirable effects Quality of evidence Values and preferences Costs of the intervention	

RCT = Randomised controlled trial.

Recommendations

1. All patients where meningitis and/or meningococcal sepsis is suspected in the community should be referred to hospital for further evaluation and consideration of a lumbar puncture (1C)
2. Rapid admission to hospital, via an emergency ambulance, should be arranged so that, where possible, the patient arrives within an hour of being assessed in the community (AR)
3. Presence or absence of headache, altered mental status, neck stiffness, fever, rash (of any description), seizures and any signs of shock (e.g. hypotension, poor capillary refill time) should be documented (1C)
4. Kernig's sign and Brudzinski's sign should not be relied upon for diagnosis (2B)

Rationale

The diagnosis of meningitis and meningococcal sepsis may seem relatively straightforward in patients with classical features of fever, headache, neck stiffness and altered mental status in the case of meningitis or fever, purpuric rash and shock in meningococcal sepsis but in many patients some of these signs will be absent.[9,24,25] The problem for general practitioners and acute physicians is to identify, from the large number of patients who present with symptoms consistent with meningitis or meningococcal sepsis, the small minority of patients who do in fact have these conditions and require urgent investigation and management.

Clinical features of meningitis

Urgent hospital referral is mandatory in adults in whom meningitis or meningococcal sepsis is suspected in view of the possibility of rapid deterioration. The individual common clinical signs such as fever, vomiting, headache and neck stiffness occur frequently in primary care and taken independently are poor discriminators for meningitis.[26] Combinations of symptoms and signs may be more useful at identifying serious disease. Although bacterial meningitis is of greater concern, clinical features alone cannot distinguish between viral and bacterial disease and in specific populations, such as the elderly or immunocompromised, the clinical presentation may be different. For example, the elderly are more likely to have an altered conscious level than their younger counterparts and less likely to have neck stiffness or fever.[27–29] Age can also be an indicator of the likely causative agent. Listeria or pneumococcal disease is more common in older people, viral meningitis commonly occurs in adults in their 20s–40s and meningococcal infection in adolescents and young adults.[5,14,27]

In the largest single published study on bacterial meningitis in adults Van de Beek and colleagues describe the clinical and laboratory features in 696 episodes of bacterial meningitis.[9] The 'classic triad' of neck stiffness, fever and altered consciousness was present in less than 50% of cases.[9] Other studies have shown similar findings.[24,30,31] Patients with pneumococcal disease are more likely to have seizures, focal neurological symptoms and a reduced conscious level (as determined by the Glasgow Coma Scale (GCS)). When a rash was present in the context of meningitis, the causative organism was *Neisseria meningitidis* in 92% of cases (the rash was petechial in 89% of these). However, 37% of cases of meningococcal meningitis patients did not have a rash. Kernig's and Brudzinski's signs are not helpful in the clinical diagnosis of suspected meningitis; they have been reported to have high specificity (up to 95%) but the sensitivity can be as low as 5%.[24,32–35] As the clinical features are often not clear cut, concern from

either the referring doctor or a relative should always be taken seriously.[36]

In addition to the above, a history of travel, the presence of a source of infection such as otitis media or sinusitis, or contact with another person with meningitis or sepsis should be ascertained.

Additional features of meningococcal sepsis and shock

Meningitis is the commonest presentation of meningococcal disease, occurring in about 60% of patients. 10–20% of patients may have evidence of shock or fulminant sepsis with or without meningitis and up to 30% of patients may have mild disease with just fever and a rash with no evidence of either meningitis or shock.[37] Meningococcal sepsis can present with hypotension, altered mental state and rash; typically this is purpuric or petechial in nature but it may take other forms including a maculopapular rash. Patients with meningococcal sepsis can deteriorate rapidly, and shock ensues; they must be monitored frequently even if they initially look well.

Shock in meningococcal sepsis results from a combination of hypovolaemia (caused by capillary leak syndrome), myocardial dysfunction, altered vasomotor tone and in some instances, adrenal insufficiency.[38,39] The clinical features of shock arise because perfusion of the vital organs (such as the brain and heart) is maintained at the expense of perfusion of the skin, kidneys and gut. In the early phases of shock these processes compensate for hypovolaemia and maintain central circulating blood volume, blood pressure and cardiac output. As a result, patients with meningococcal sepsis often present with cold peripheries and prolonged capillary refill time as well as oliguria. In the most severe cases, ischaemia of the skin or even whole limbs may occur, particularly if there is thrombosis in areas of vascular stasis. In addition, many patients with septic shock will develop renal dysfunction, often leading to acute kidney injury.[11] The pathophysiology is fully reviewed by Pathan and colleagues.[40]

Despite severe shock, in healthy young people and adolescents preservation of brain perfusion and function is often maintained until relatively late, so that the young person's relatively alert state may make nursing and medical staff under-estimate the degree of cardiovascular collapse. Eventually cerebral dysfunction indicates loss of cerebral vascular homeostasis and reduced brain perfusion.

Box 4. Risk factors for a fatal outcome in meningococcal disease.

Rapidly progressing rash
Coma
Hypotension and shock
Lactate >4 mmol/L
Low/normal peripheral white blood cell count
Low acute phase reactants
Low platelets
Coagulopathy
Absence of meningitis

The onset of hypotension signifies a failure of the compensatory mechanisms. It should be remembered that shock in young people is not always accompanied by the presence of arterial hypotension (cryptic shock), but may be indicated by the presence of a high blood lactate level (>4 mmol/L). Risk factors for a fatal outcome in meningococcal sepsis are shown in Box 4.

The Surviving Sepsis guidelines also provide additional guidance on the management of patients with suspected sepsis.[41]

Should antibiotics be given prior to admission?

Recommendations

5. Antibiotics should be given to patients in the community in whom there are signs of meningococcal disease e.g. a rash in combination with signs of meningism or severe sepsis (1D)
6. Antibiotics should be given to patients in the community in whom there are signs of severe sepsis e.g. hypotension, poor capillary refill time, altered mental state (1D)
7. Antibiotics should be given to patients in the community, with suspected meningitis, who will have a delay of more than one hour in getting to hospital (2D)
8. If antibiotics are given in the community they should be in the form of Benzylpenicillin 1200 mg IM or IV, or a third generation cephalosporin such as Cefotaxime (2 g) or Ceftriaxone (2 g) IM or IV (1C)
9. In the case of known anaphylaxis to penicillins or cephalosporins, antibiotics should not be given until admission to hospital (AR)
10. The administration of parenteral antibiotics should not delay transfer to hospital (1D)

Rationale

The aim of pre-hospital antibiotics is to reduce the mortality associated with delays in antibiotic therapy.[42–45] However there are some drawbacks to this approach; these include the risk of allergic reaction to the antibiotic and the need to consider concurrent steroid administration to reduce complications associated with pneumococcal meningitis. In addition, antibiotic treatment before lumbar puncture (LP) can alter the initial diagnostic investigations, reducing the likelihood of identifying bacteria from cerebrospinal fluid (CSF) culture, and may lead to the misdiagnosis of bacterial meningitis as viral.[46,47] Molecular diagnostics such as the polymerase chain reaction (PCR), can detect pathogens up to 9 days after antibiotics have been given[48,49] but they do not give antibiotic susceptibilities which remain vital.

Two systematic reviews investigating pre-hospital antibiotics in meningococcal meningitis have been carried out in recent years.[50,51] One[50] only identified a single trial, based during an epidemic in Niger, that met their inclusion criteria of randomised (or quasi randomised) controlled trials comparing antibiotics with placebo/no intervention.[52] The other identified 14 studies, all of which were observational. The studies used oral or parenteral antibiotics and five stratified by disease severity. Overall these systematic

reviews do not provide evidence for or against the use of pre-hospital antibiotics and it is unlikely further randomised controlled trials will be undertaken. However, given the evidence that in general early antibiotics reduce mortality, it would seem prudent that they are used as soon as possible in patients with a strong suspicion of bacterial meningitis, especially if there are signs indicative of a worse outcome,[53] or where there may be a delay in hospital admission. Pre-hospital antibiotics should also be given if the patient is thought to have meningococcal disease in view of the potential for rapid catastrophic deterioration. If antibiotics are given in the community this must not delay hospital admission. As benzylpenicillin, cefotaxime and ceftriaxone have good CSF penetration in inflamed meninges and can be given via the intramuscular route as well as intravenously they are good options for use in the community. If there is known anaphylaxis to these beta-lactam antibiotics, treatment should be delayed until admission to hospital when appropriate antibiotics can be given.

Immediate action within the first hour of arriving at hospital

What should the initial hospital assessment and immediate action be?

Recommendations

11. Stabilisation of the patient's airway, breathing and circulation should be an immediate priority (AR).
12. A decision regarding the need for senior review and/or intensive care admission should be made within the first hour (AR).
13. The patient's conscious level should be documented using the Glasgow coma scale (2C).
14. Blood cultures should be taken as soon as possible and within 1 h of arrival at hospital (AR)
15. In patients with suspected meningitis (with no signs of shock or severe sepsis)
    - LP should be performed within 1 h of arrival at hospital provided that it is safe to do so (1D)
    - treatment should be commenced immediately after the LP has been performed, and within the first hour (1B)
    - If the LP cannot be performed within 1 h treatment should be commenced immediately after blood cultures have been taken and LP performed as soon as possible after that (1B)
16. In patients with predominantly sepsis or a rapidly evolving rash:
    - Antibiotics should be given immediately after blood cultures have been taken (AR)
    - Fluid resuscitation should be commenced immediately with an initial bolus of 500 ml of crystalloid (1B)
    - The Surviving sepsis guidelines should be followed (AR)
    - LP should not be performed at this time (1D)
17. All clinicians managing such patients should have postgraduate training on the initial management of acute bacterial meningitis and meningococcal sepsis [AR]
18. Patients with meningitis and meningococcal sepsis should be cared for with the input of an infection specialist such as a microbiologist or a physician with training in infectious diseases and/or microbiology [AR].

Rationale

The priority for patients admitted with suspected meningitis is to a) stabilise their airway, breathing and circulation, b) begin appropriate investigations, and c) instigate prompt treatment. These three things should largely happen concurrently. All patients should be reviewed by a senior clinician. The Royal College of Physicians recommend consultant review for all acute medical patients within 14 h of admission. Most patients with suspected meningitis or meningococcal sepsis should be seen much earlier than this. The need for urgent review should be assessed early using the National Early Warning Score.[54] An aggregate score of 5/6 (or a score of 3 in any single physiological parameter) should prompt an urgent review by a clinician competent to assess acutely ill patients; a score of 7 or more should prompt an urgent assessment by a team with critical care competencies. Clinicians should, however, not be falsely reassured if the early warning score is lower than these parameters, because patients with meningitis, and meningococcal sepsis in particular, can deteriorate rapidly. In addition the presence or absence of a rash and the use of pre-admission antibiotics should be recorded for all patients. The GCS should be recorded both for its prognostic value, and to allow changes to be monitored. A GCS of $\leq$8 is associated with a poor outcome.[55] The GCS also helps with decisions about whether it is safe to perform a LP (see Box 5). Blood cultures should be taken as soon as possible and certainly within 1 h of presentation, prior to the prompt administration of antibiotics.[41]

Patients with suspected meningitis (without shock or any signs of meningococcal sepsis)

Ideally the LP should also be performed before starting antibiotics in order to allow the best chance of a definitive diagnosis. This may require the equipment, facilities and personnel to carry out LPs to be available within the

Box 5. Indications for neuroimaging before lumbar puncture (LP) in suspected meningitis*.

- **Focal neurological signs**
- **Presence of papilloedema****
- **Continuous or uncontrolled seizures**
- **GCS ≤ 12*****

*to exclude significant brain swelling and shift that may predispose to cerebral herniation post LP.
**inability to view the fundus is not a contraindication to LP, especially in patients who have had a short duration of symptoms.
*** LP without prior neuroimaging may be safe at levels below this.

Box 6. Initial therapeutic endpoints in the resuscitation of septic shock[41]

Capillary refill time less than 2 s
Normal blood pressure for age (in adults > 65 mmHg mean BP)
Normal pulses with no differential between peripheral and central pulses
Warm extremities
Urine output >0.5 ml/kg/hour (A urinary catheter is required)
Normal mental status
Central venous pressure 8–12 mmHg
Lactate < 2 mmol/L

emergency department. The need for a rapid LP has to be weighed against the desire to start antimicrobial treatment urgently.[56] Even if treatment has been initiated, a LP should still be performed as soon as possible, preferably within 4 h of commencing antibiotics, to help identify the cause of meningitis. The culture rate can drop off rapidly after that time and it can become difficult to identify the causative bacteria in cases of bacterial meningitis.[56] Intravenous antibiotics should be given promptly in hospital as there is evidence that delays increase mortality.[43–45]

Patients with suspected meningococcal sepsis, suspected meningitis with shock or a rapidly evolving rash

In patients with suspected meningococcal sepsis, or meningitis with shock, the priority is circulatory stabilization although there is conflicting evidence surrounding the amount and type of fluid to be used. In shocked patients fluid resuscitation should be given carefully in boluses of 500 ml monitoring the patient for fluid overload with an initial fluid bolus of 500 ml of crystalloid given rapidly (over 5–10 min). Shock may be rapidly reversed by this initial fluid bolus, but repeated review is necessary. In such critically ill patients careful fluid resuscitation should continue, aiming to achieve the therapeutic endpoints for surviving sepsis shown in Box 6.[41] Vasopressors may be necessary if shock does not respond to initial fluid challenges but this should be instituted in a critical care setting. In keeping with international guidance on the management of sepsis, if there are any signs of severe sepsis or septic shock antibiotics should be given immediately and certainly within the first hour.[41]

Bacterial meningitis and meningococcal sepsis are rare medical emergencies. Therefore, it is essential that all doctors who may encounter a case are adequately trained. In addition specialists in the management of infectious diseases should be consulted early as there is some observational evidence that patient outcomes are improved if they are managed by a specialist.[56]

Lumbar punctures and imaging

Which patients with suspected meningitis should have a lumbar puncture (LP)?

Recommendations

1. Patients should not have neuroimaging before their LP unless there is a clinical indication suggestive of brain shift (see Box 5) (1D)
2. If prior neuroimaging is indicated an LP should be performed as soon as possible after the neuroimaging unless:
   a. neuroimaging reveals significant brain shift (1D)
   b. An alternative diagnosis is established (AR)
   c. The patient's clinical condition precludes an LP by having continued seizures, rapidly deteriorating GCS or cardiac/respiratory compromise (AR)
3. Regardless of neuroimaging considerations LP should be delayed/avoided in the following situations (AR):
   a Respiratory or cardiac compromise
   b. Signs of severe sepsis or a rapidly evolving rash
   c. Infection at the site of the LP
   d. A coagulopathy

When should a lumbar puncture be performed in patients who are on anticoagulants?

Recommendations

4. If a neurological infection is suspected on admission prophylactic subcutaneous low molecular weight heparin (LMWH) should not be started until 4 h after the LP is performed (AR)
5. In patients already on prophylactic LMWH the LP should not be performed until 12 h after the dose (AR)
6. Prophylactic LMWH should be delayed until 4 h after a LP (AR)
7. Patients on therapeutic LMWH should not have an LP until 24 h after a dose (AR)
8. Therapeutic intravenous unfractionated heparin can be restarted 1 h after an LP (2C)
9. In patients on warfarin LP should not be performed until INR is ≤1.4 (2D)
10. Patients on aspirin and other non-steroidal anti-inflammatories do not need to have their LP delayed (1C)
11. In patients on clopidogrel an LP should be delayed for 7 days or until a platelet transfusion or desmopressin (DDAVP) is given – these should be discussed with a haematologist and the risk benefit ratio of performing a LP discussed (AR)
12. Expert advice, from a haematologist, must be sought for those patients on newer anticoagulants such as apixaban, dabigatran etexilate and rivaroxaban (AR)
13. In patients with known thrombocytopenia LP should not be performed at platelet counts of $<40 \times 10^9$/L or with a rapidly falling platelet count (1D)
14. LP should not be delayed for the results of blood tests unless there is a high clinical suspicion of a bleeding diathesis (AR)
15. In situations where a LP is not possible immediately, this should be reviewed at 12 h and regularly thereafter (AR)

Should diagnostic scoring systems be used?

16. Diagnostic scoring systems are not recommended (1D).

Rationale

A LP is an essential investigation in the management of patients with suspected meningitis. In the majority of patients this can be performed without prior neuroimaging, though this has been a controversial area.[57–60] Performing a CT scan before the LP is associated with delays in antibiotics, which in turn can lead to an increase in mortality.[15,43] A CT scan should only be performed if there are clinical signs suggestive of a shift of brain compartments. This is because there is a theoretical risk that a lumbar puncture, by lowering the pressure, might make such shift worse, resulting in a brain herniation syndrome. If there are signs suggestive of brain shift, the CT scan may identify any space occupying lesions, brain swelling or shift, although these may occur in the context of a normal brain CT.[59] The CT scan does not detect raised intracranial pressure. The clinical features indicative of a possible shift of brain compartments include focal neurological signs and a reduced GCS (Box 5). The exact level of GCS at which a CT scan is indicated is debated.[9,21,57–59,61,62] A range of values has been suggested ranging from a GCS of <8 to <13.[63,64] Some guidelines just state 'abnormal level of consciousness',[65] meaning obtunded/not alert or unresponsive.[59] We recommend that an LP can be performed without prior neuroimaging if the GCS is >12 and may be safer at lower levels. Those with a GCS ≤ 12 will require a brain scan but should first be assessed by a critical care physician and intubation may be considered.

Of note, in 2009, the Swedish guidelines for the management of meningitis changed their recommendations and removed altered conscious level as an indication for CT before LP. A subsequent study compared the management of approximately 400 patients before and 300 after the change in guidelines; it showed that after the change, antimicrobial treatment was started on average 1.2 h earlier, and the mortality was lower, (6.9% vs 11.7%) with a lower risk of sequelae (38% vs 49%).[66] Whilst there may have been other changes implemented during this time period that led to the improved outcomes it does support the fact that patients do not suffer excess harm or mortality when an LP is performed without a CT scan.

Some authorities also suggest 'immunocompromise' as a reason to perform a CT scan before an LP. Whilst we recognise that immunocompromised patients may be more at risk of intracranial mass lesions we find no evidence that they would be at any increased risk of cerebral herniation if they presented without the clinical signs indicated in Box 5.

If neurological imaging is performed and no contraindication is found the LP should be performed as soon as possible afterwards (unless an alternative diagnosis has been made in the interim).

Lumbar puncture and clotting abnormalities

Subdural haematoma is a potential complication of an LP; although the exact incidence of post-LP haematomas is unknown the risk is increased if the LP is performed in patients with abnormal clotting. However, there is little objective evidence on which to guide safe clotting parameters for LP in patients with neurological infections. In line with the UK Department of Health's recommendations on venothromboembolic disease[67] we recommend for patients already on prophylactic LMWH the LP should not be performed until 12 h after the last dose. If patients have not commenced on LMWH the LP should be performed as soon as possible and prophylactic LMWH can be started 4 h afterwards. The duration of action of LMWH will be longer in patients with severe renal impairment and coagulation parameters such as the APTTr, may need to be checked in such cases.[67,68] For patients who are on higher doses of LMWH an LP should not be performed within 24 h of therapeutic LMWH.[69]

There have been large observational studies evaluating unfractionated heparin and spinal or epidural anaesthesia. In these studies the risk of spinal haematomas was negligible in patients in whom the heparin was given after at least 60 min.[70,71] Extrapolating from this we recommend that unfractionated heparin can be restarted 1 h after an LP.

In patients on warfarin the risks of reversing the warfarin will need to be weighed against the benefits of performing an LP. An LP should not be routinely performed at an INR of ≥ 1.5.[72,73] Therapy with aspirin or non-steroidal anti-inflammatory medications alone does not increase the risk of spinal haematoma after LP[74] and LP does not need to be delayed in patients who are taking these drugs. Clopidogrel inhibits platelet aggregation for the whole lifespan of the platelet which is between 7 and 10 days.[75] If the benefits of performing the LP are deemed to outweigh the risks, in consultation with a haematologist, a platelet transfusion can be given 6–8 h after the last dose of clopidogrel) prior to LP. Patients receiving the newer oral anticoagulants such as apixaban, dabigatran etexilate and rivaroxaban should be discussed with a haematologist. Trials are ongoing regarding specific reversal agents for these drugs and a monoclonal antibody fragment, specifically aimed at dabigatran, has recently been approved by the European Medicines Agency.[76] There may be a role for reversal agents prior to LP in the future but these cases should be discussed with a specialist.

The evidence regarding a platelet count at which it is safe to perform a LP mostly comes from patients with haematological malignancies, obstetric patients and patients requiring regional anaesthesia. The risk of the procedure must be balanced against the benefits of having a definitive diagnosis. A recent review of the literature by van Veen has suggested that a platelet count of $>40 \times 10^9$/L is safe and that even lower counts may be acceptable, depending on the individual case.[77] In addition to the absolute platelet count both the trend and the cause of thrombocytopenia must be taken into consideration: a rapidly falling platelet count is likely to be a higher risk than a stable thrombocytopenia; similarly, thrombocytopenia secondary to chronic idiopathic thrombocytopenic purpura probably carries a lower risk than thrombocytopenia due to DIC. The majority of the studies (five of seven) identified in van Veen's review were in paediatrics, and all were in patients with cancer and not infection. In the patients who developed complications after LP this was almost always in the presence of another risk factor such as rapidly falling platelet count, other coagulopathy or traumatic LP. Unless there is a strong suspicion that the patient will have a clotting abnormality the LP should not be delayed to await the results of blood tests.

If there is any reason to delay the LP initially this decision should be reviewed regularly and consideration given to performing the procedure later if the diagnosis has not been confirmed by other means.

A low pressure type headache is a much more common complication following LP and can occur in up to a third of patients.[78] Some methods and myths associated with the prevention of a post LP headache are shown in Box 7.

Diagnostic scoring systems

Several scoring systems have been developed to try and help clinicians differentiate bacterial meningitis from other forms of meningitis, especially viral, based mostly on the initial CSF findings.[79–87] This is because CSF culture results can take some time, and an early indicator, based on initial CSF results, would allow unnecessary antibiotics to be stopped and patients deemed to have viral meningitis to be discharged. In addition to requiring CSF data, many rely on plasma glucose, which is often not performed; while others require complex calculations which are impractical in a busy acute medical setting. Most have been developed in paediatric settings, only been tested retrospectively and have not been externally validated although there has been a recent score developed prospectively for adults[87]). No clinical predictor tool has been widely translated to use in routine clinical practice and we do not recommend their use.

Investigations

Laboratory investigations help establish the aetiology of meningitis and sepsis, especially differentiating between viral and bacterial causes, identify antibiotic resistant organisms, assist with prognosis and guide public health management including infection control, immunisation for the patient and contacts, and antibiotic prophylaxis (Fig. 1).

What investigations should be performed for suspected meningitis or meningococcal sepsis?

Recommendations

1. In all patients with suspected meningitis and/or meningococcal sepsis blood should be sent for:
   a. Culture (prior to antibiotics wherever possible) (1C).
   b. If antibiotics have been given in the community blood cultures should be taken as soon as possible on arrival in hospital (within the first hour) (1C)
   c. Pneumococcal and meningococcal PCR (EDTA sample) (1C)
   d. Storage, to enable serological testing if a cause is not identified (a convalescent serum sample should also be sent 4–6 weeks later – discuss with microbiologist) [1C]
   e. Glucose measurement (1C)
   f. Lactate measurement (1C)
   g. Procalcitonin (if available) (2C)
   h. Full blood count, urea, creatinine, electrolytes, liver function tests and clotting screen
2. In all patients in whom a LP is performed the following should be documented/requested: [1C]
   a. CSF opening pressure (unless the LP is performed in the sitting position).
   b. CSF glucose with concurrent plasma glucose
   c. CSF protein
   d. CSF lactate (if prior antibiotics have not been given) (2B)
   e. CSF for microscopy, culture and sensitivities
3. CSF PCR for pneumococci and meningococci should be performed in all cases of suspected bacterial meningitis[1C]
4. CSF should be stored for later tests if initial investigations do not yield a pathogen [1C]
5. A swab of the posterior nasopharyngeal wall should be obtained as soon as possible, and sent for meningococcal culture, in all cases of suspected meningococcal meningitis/sepsis [1C]
6. Any significant bacterial isolates (including meningococci identified from the nasopharynx) should be sent to the relevant national reference laboratory for serotyping [1C]

Rationale

Blood tests

Blood cultures should be taken in all cases of suspected bacterial meningitis or meningococcal sepsis. Ideally this should be before any antibiotics are given, when the yield can be as high as 74%. If a patient received antibiotics before hospital admission, blood cultures should be taken as soon as possible after arrival in hospital. Non-culture diagnostics approaches to pathogen identification, such as PCR, are becoming increasingly important. PCR of peripheral blood increases the laboratory confirmation rate in meningococcal disease substantially, especially as it will remain positive for several days after antibiotics have been initiated.[88] There are fewer data on the sensitivity and specificity of blood PCR in patients with pneumococcal meningitis, though a small paediatric study showed it to be useful,[89] and a multiplex PCR was highly sensitive in another study.[90] There is a concern that in children PCR of blood for pneumococci can be positive without evidence of invasive disease, presumably because of asymptomatic carriage,[91] the same has not been shown in adults. However, in adults with features of bacterial meningitis a positive PCR in the blood can be a useful adjunct for diagnosing the aetiological cause.

Serological assays may also play a role in the diagnosis of meningitis caused by mumps, syphilis or Lyme disease for example. If no pathogen is identified on first line testing, an acute serum sample should be taken and stored and a convalescent sample taken at 4–6 weeks. These tests should be discussed with local infection specialists.

Glucose must be taken at the same time as the LP in order to allow interpretation of the CSF glucose. Lactate measurement is useful in the management of anyone with suspected sepsis and if raised can provide useful guidance for resuscitation (Box 6).

Serum procalcitonin can be helpful for the differentiation of bacterial and viral infections. It has a sensitivity of 95% and a specificity of 100% (PPV – 97–100%; NPV – 93.9–100%) for distinguishing bacterial meningitis from viral in adults.[92,93] Its routine use is limited by its availability and cost although a recent meta-analysis has suggested it might be cost effective in the paediatric setting.[94] A recent technology assessment by the UK National Institute

Box 7. Methods to reduce headache post lumbar puncture.

Definition and aetiology

Headache following a lumbar puncture (LP) typically has a low-pressure phenotype; i.e. worse upright and better lying flat. It is usually caused by a dural tear sustained at the time of LP and does not relate to the volume of cerebrospinal fluid (CSF) taken. In most cases it is self-limiting although a few patients may require a blood patch for persistent headache, and rarely the low pressure may be associated with the development of subdural haematomas.

Practices associated with reduced risk of post-LP headache

1. Finer gauge needles[274,275]
2. Risk of headache decreases with smaller gauge needles, but this needs to be balanced with the length of time the procedure will take with a very fine needle. Practically a 22G needle is probably the smallest that can be used.
3. Non-traumatic (less traumatic) needles[275,279]
   - Paraesthesia rate and failure rate may be higher with these needles
4. Orientation of the bevel of the needle in a transverse plane (perpendicular to the longitudinal axis)[277,278]
   - This is probably less important if an atraumatic needle is being used.
5. Replacement of the stylet before withdrawing the needle[280]
6. Experience of performing LPs and number of attempts at LP[281]
   - Fewer attempts at dural puncture is thought to be associated with a decreased incidence of headache after lumbar puncture.

Practices **NOT** proven to reduce risk of post LP headache

1. Reducing the volume of CSF taken[282]
   - There is no evidence that the amount of CSF removed influences the incidence of post LP headache
2. Bed rest[283,284]
   - Patients are often advised to lie recumbent for a period of time after an LP but there is no evidence that this reduces the risk of headache.
3. Hydration[285]
   - There has only been one study looking at fluid post LP as a preventative strategy and it showed no difference between those who took 1.5 L and those who had 3 L post LP.
4. Caffeine
   - There have been some experiments looking at IV caffeine to *treat* post LP headache but there is no evidence that either oral or IV caffeine can prevent the headache.

of Health and Care Excellence (NICE) has found that whilst procalcitonin assays show promise there is currently insufficient evidence to recommend routine adoption into the NHS. However, it should be noted that they did not consider any studies looking at meningitis. They also accepted that some centres do use procalcitonin to guide management — these centres were encouraged to take part in relevant data collection and research. As a result we continue to recommend the use of procalcitonin if it is available.[95]

CSF

Initial CSF analysis of cells protein and glucose helps determine the likely cause of meningitis; subsequent microscopy and culture can confirm the aetiology and antibiotic susceptibilities. The use of pre-prepared LP packs, with all the necessary sampling tubes may increase the diagnostic yield.[96] Often inappropriately small volumes of CSF are taken limiting the number of investigations that can be performed. As CSF is produced at a rate of approximately 22 ml/h (similar to urine) amounts of at least 15 ml can be safely removed from adults.[97,98]

CSF opening pressure should always be measured when doing a lumbar puncture (unless it is done in the sitting position, when it will be artificially raised because of the positioning). The opening pressure is normally elevated above 20 cm CSF in bacterial meningitis, and is often higher.[9]

CSF cell count

In acute bacterial meningitis there is classically a polymorphonuclear pleocytosis in the CSF (see Table 4) but there are always exceptions to the rule. There can be minimal, even no white cells, especially early on in the course of the illness; in one study 10% of patients had fewer than 100 cells per mm^3.[9,99,100] There may be a predominance of lymphocytes in some cases of bacterial meningitis e.g. listeria or partially treated bacterial meningitis.[101] A predominance of neutrophils may also be seen in early viral meningitis,[102] especially enteroviral disease, although such patients are unlikely to have a total CSF white cell count of over 2000 cells per mm^3.[81]

CSF biochemistry

The CSF glucose, protein and lactate are all useful for differentiating viral, bacterial and other causes of meningitis. The values can give valuable pointers to the likely

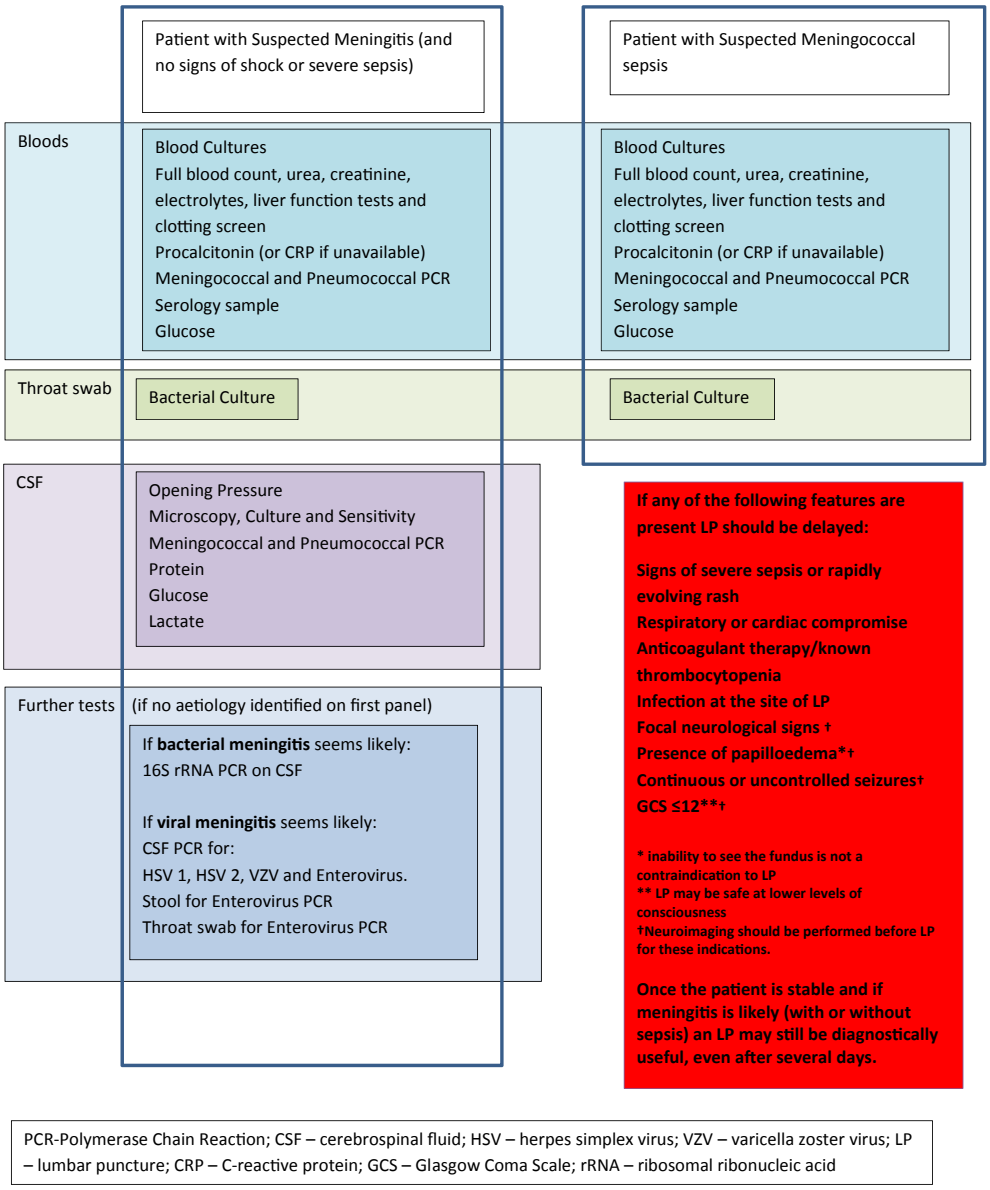

Figure 1 Investigations algorithm.

aetiology but are not usually definitive because of overlap between the different diseases. Bacterial meningitis tends to have a higher CSF protein than viral meningitis and one study found that a patient is unlikely to have bacterial disease if the CSF protein is less than 0.6 g/L.[103] The CSF glucose is lowered in bacterial meningitis; however the concentration also varies according to the plasma glucose and so the CSF:plasma glucose ratio should be used. Normally CSF glucose is about two thirds of the plasma glucose. In bacterial meningitis the ratio is usually significantly lower than this, a CSF:plasma glucose ratio cut off of 0.36 for diagnosing bacterial meningitis has a high sensitivity and specificity (93%).[104] Unfortunately plasma glucose is often not performed in clinical practice, and so the CSF glucose must be interpreted in isolation. One report suggest a CSF glucose of above 2.6 mmol/L is unlikely to be associated with bacterial meningitis.[105] No CSF parameters give an absolute indication of cause, and any CSF results must be interpreted in the context of the clinical presentation.

CSF lactate has a high sensitivity and specificity (93% and 96% respectively) in distinguishing between bacterial and viral meningitis if antibiotics had not been given beforehand. A CSF lactate cut off of 35 mg/dl has been suggested to have the best sensitivity for distinguishing between bacterial and viral meningitis. If patients have received antibiotics the sensitivity drops to less than 50%.[106] The high negative predictive value makes it a useful test, if done prior to commencing antibiotics, to rule out bacterial meningitis and reassurance to stop or withhold antibiotics.

CSF gram stain and culture

Gram stain of the CSF is a rapid method for detecting bacteria with a sensitivity of between 50 and 99% (dependent on organism and prior antibiotics) and a specificity of

Table 4 Classical CSF Features of the different causes of meningitis.

	Normal	Bacterial	Viral	Tuberculous	Fungal
Opening Pressure (cm CSF)	12–20	Raised	Normal/mildly raised	Raised	Raised
Appearance	Clear	Turbid, cloudy, purulent	Clear	Clear or cloudy	Clear or cloudy
CSF WCC (cells/uL)	<5	Raised (typically >100)[a]	Raised (typically 5–1000)[a]	Raised (typically 5–500)[a]	Raised (typically 5–500)[a]
Predominant cell type	n/a	Neutrophils[b]	Lymphocytes[c]	Lymphocytes[d]	Lymphocytes
CSF protein (g/L)	<0.4	Raised	Mildly raised	Markedly raised	Raised
CSF glucose (mmol)	2.6–4.5	Very low	Normal/slightly low	Very low	Low
CSF/plasma glucose ratio	>0.66	Very low	Normal/slightly low	Very low	Low

CSF – cerebrospinal fluid; WCC – white cell count.
Local laboratory ranges for biochemical tests should be consulted and may vary from these quoted here.
A traumatic lumbar puncture will affect the results by falsely elevating the white cells due to excessive red cells. A common correction factor used is 1:1000.
[a] Occasionally the CSF WCC may be normal (especially in immunodeficiency or tuberculous meningitis).
[b] May be lymphocytic if antibiotics given before lumbar puncture (partially treated bacterial meningitis), or with certain bacteria e.g. *Listeria monocytogenes*.
[c] May be neutrophilic in enteroviral meningitis (especially early in disease).
[d] May be neutrophils early on in the course of disease.

97–100%.[9] Cytospin centrifugation of CSF can increase the yield.[107] The gold standard for the diagnosis of bacterial meningitis is CSF culture. Depending on whether prior antibiotics have not been given, and depending on the infecting organism, it is diagnostic in 70–85% of cases of bacterial meningitis.[108] CSF sterilization may occur within the first 2 h of administration of antibiotics for meningococci and within 4 h for pneumococci.[109] However, even if rendered culture negative, CSF analysis may be helpful up to 48 h after commencing parenteral antibiotics.

CSF PCR

CSF PCR can rapidly identify the causative organism in meningitis and is especially useful if antibiotics have been given prior to LP. PCR has a sensitivity of 87–100% and specificity of 98–100%[110–113]. If an organism cannot be identified by pathogen specific PCR, then PCR for 16S ribosomal RNA, which is present in almost all bacteria may be used, although it has lower specificity.[114] Multiplex PCR and other platforms that can detect multiple pathogens at the same time are increasingly being trialled and can reduce time and increase sensitivity.[115–117] We would recommend that each diagnostic laboratory evaluate any tests prior to use.

Latex agglutination tests

The bacteria commonly causing meningitis carry specific polysaccharide surface antigens that can be detected by agglutination tests on the CSF. They have largely been surpassed by the use PCR and are not recommended except in large outbreak situations where rapid PCR is not available.

Some CSF should also be stored in order to be used for further investigations if necessary.

Nasopharyngeal isolates

Meningococci can be isolated from the nasopharynx in up to 50% of patients with meningococcal disease. If patients have started antibiotics nasal swabs may still be positive when blood and CSF cultures are negative, although these data predates the widespread use of empirical cephalosporins.[118] Given that many patients are diagnosed by PCR alone (in the blood and/or CSF), without a cultured isolate, nasopharyngeal swabs should be taken to attempt to grow an organism which is important for surveillance and determination of vaccine coverage. Such isolates are almost always identical to those from their blood or CSF (when culture of these samples has been successful)[119,120] but the possibility of asymptomatic and irrelevant carriage should be considered – especially if the clinical picture is not compatible with acute meningococcal meningitis. All significant isolates (from any site) should be referred to the relevant reference laboratory.

Streptococcus pneumoniae is also carried asymptomatically in the nose but there are often multiple strains and it is not clear that the strain in the nose is definitely related to that which causes meningitis, hence nasal swabbing is not recommended for pneumococcal disease.

Treatment

What antibiotic treatment should be given empirically? (Table 5 and Fig. 2)

Recommendations

1. All patients with suspected meningitis or meningococcal sepsis should be given 2 g ceftriaxone intravenously (IV) every 12-h or 2 g cefotaxime IV every 6-h [1B]
2. If the patient has, within the last 6 months, been to a country where penicillin resistant pneumococci are prevalent, IV vancomycin 15–20 mg/kg should be added 12-hourly (or 600 mg rifampicin 12-hourly IV or orally) [1C]

3. Those aged 60 or over should receive 2 g IV ampicillin/amoxicillin 4-hourly in addition to a cephalosporin [1B].
4. Immunocompromised patients (including diabetics and those with a history of alcohol misuse) should receive 2 g IV ampicillin/amoxicillin 4-hourly in addition to a cephalosporin [1B].
5. If there is a clear history of anaphylaxis to penicillins or cephalosporins give IV chloramphenicol 25 mg/kg 6-hourly [1C]

Rationale

The choice of antibiotics in patients with bacterial meningitis is a three stage process, with initial empirical decisions based on clinical suspicion, modified once CSF Gram stain is available, and then again if CSF culture results are positive. Antimicrobial penetration into the CSF is dependent on lipid solubility, molecular size, capillary and choroid plexus efflux pumps, protein binding, and the degree of inflammation of the meninges.[121] Although there is little high quality trial evidence to guide the antibiotics used in suspected meningitis and meningococcal sepsis the choice of empirical antibiotic is based largely on known pharmacokinetics, the likely infecting organism and known or suspected antimicrobial resistance patterns. Third generation cephalosporins[122] have known bactericidal activity for both pneumococci and meningococci and penetrate inflamed meninges; as such they are the empirical antibiotic of choice in most settings where resistance rates are low.

Rates of pneumococcal resistance to penicillin in the UK are low, but a travel history may indicate that a patient with meningitis has recently been in a country with high rates of pneumococcal resistance (Box 8). If a patient has visited such a country in the last 6 months, then vancomycin or rifampicin should be added to the empirical antibiotics. Up to date European and worldwide data on resistance can be found via the European Centre for Disease Prevention and Control website or the World Health Organisation (http://bit.ly/1Kosckx and http://bit.ly/1rOb3cx). Although meningococci with reduced susceptibility to penicillin have been reported, patients infected by these strains do respond to the high doses of penicillin or cephalosporins usually given in meningitis. Overt meningococcal resistance to penicillin is extremely rare.[13]

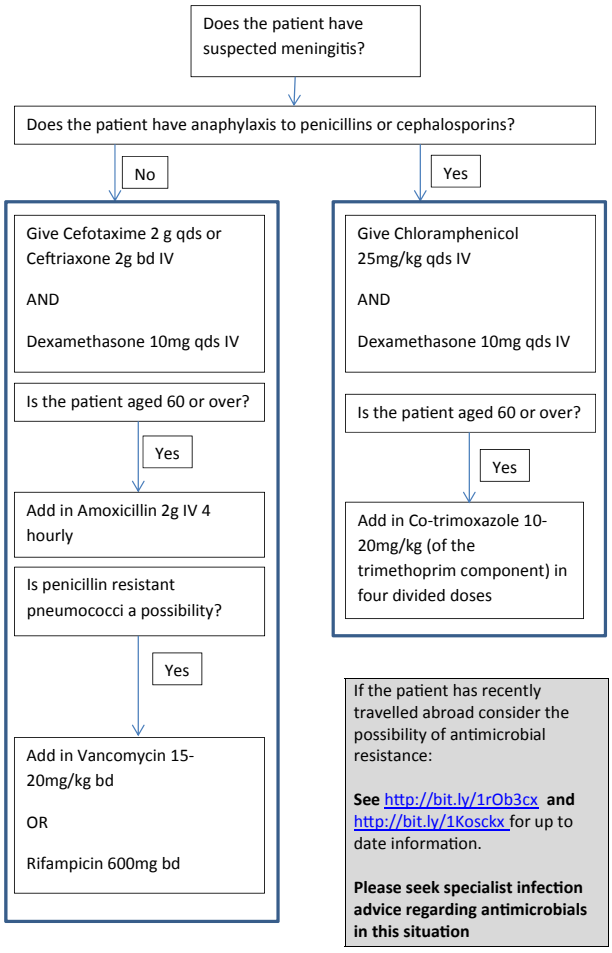

Figure 2 Algorithm for the empirical treatment of suspected meningitis.

Listeria meningitis occurs in people who are immunocompromised, have chronic illnesses such as alcohol dependency, diabetes, and malignancy, or are elderly.[123] It responds poorly to cephalosporin treatment, and so amoxicillin should be added. The age at which it should be added is debated. Although in some guidelines a cut-off of 50

Table 5 Empirical antibiotic choices.

	Preferred choice	Alternative
Adults <60 years of age[a]	Cefotaxime 2 g 6 hourly OR Ceftriaxone 2 g 12 hourly	Chloramphenicol 25 mg/kg 6 hourly
Adults ≥60 years of age[a]	Cefotaxime 2 g 6 hourly OR Ceftriaxone 2 g 12 hourly AND Amoxicillin 2 g 4 hourly	Chloramphenicol 25 mg/kg 6 hourly AND Co-trimoxazole 10—20 mg/kg (of the trimethoprim component) in four divided doses

[a] Add in IV Vancomycin 15—20 mg/kg bd or Rifampicin 600 mg bd if penicillin resistance is suspected e.g. patient has recently arrived from a country where penicillin resistant pneumococci are prevalent (if unsure, check with local infectious diseases/microbiology expertise).

Box 8. Selected countries with penicillin resistance (refer to[286] for a complete list).

Canada
China
Croatia
Greece
Italy
Mexico
Pakistan
Poland
Spain
Turkey
USA

years has been advocated,[1,65] a review of the literature has shown that *Listeria* meningitis or invasive Listeriosis in the immunocompetent adult was rare if under 60.[124–131]

Although reactions to penicillin are commonly reported by patients, a careful history should be taken as there is often little evidence for a true allergy. Alternative antibiotics should be given only when there is a clear history of anaphylaxis to penicillins or cephalosporins and the history of any alleged allergic reactions should be investigated carefully.

What definitive antimicrobial treatment should be given once microbiology results are available? (Table 6)

Recommendations

Patients with meningitis:
Treatment following CSF Gram stain result

6. If Gram-positive diplococci (likely *Streptococcus pneumoniae)* are visible on Gram stain of CSF:
   - Continue 2 g ceftriaxone IV 12 hourly or 2 g cefotaxime IV 6-hourly (AR)
   - If the patient comes from a country where penicillin resistance is common add vancomycin 15–20 mg/kg IV 12-hourly (rifampicin 600 mg IV/orally 12-hourly can be given as an alternative and should be used in patients with renal failure) until antimicrobial resistance information is available (AR)
7. If Gram-negative diplococci (likely *N. meningitidis*) are visible on Gram stain of CSF:
   - Continue 2 g ceftriaxone IV 12 hourly or 2 g cefotaxime IV 6-hourly (AR)
8. If Gram-positive bacilli suggestive of *Listeria monocytogenes* are visible on Gram stain of CSF:
   - Add ampicillin/amoxicillin 2 g 4-hourly IV (if not started empirically) (AR).
   - Continue with 2 g ceftriaxone IV 12 hourly or 2 g cefotaxime IV 6-hourly until culture confirmed (AR).
9. If Gram negative rods are visible on Gram stain:
   - Continue 2 g ceftriaxone IV 12-hourly or 2 g cefotaxime IV 6-hourly and seek specialist advice regarding local antimicrobial resistance patterns (AR)
   - If there is a high suspicion that an extended spectrum beta lactamase (ESBL) organism might be present IV Meropenem 2 g 8 hourly should be given (AR)

Treatment following positive culture or PCR result (from blood or CSF):

Pneumococcal meningitis

10. If Streptococcus pneumoniae is identified:
    - Continue with 2 g ceftriaxone IV 12 hourly or 2 g cefotaxime IV 6-hourly (AR)
    - If the pneumococcus is penicillin sensitive (MIC $\leq$ 0.06 mg/L) any of the following options would be suitable: IV benzylpenicillin 2.4 g 4 hourly, 2 g ceftriaxone IV 12 hourly or 2 g cefotaxime IV 6-hourly (AR)
    - If the pneumococcus is penicillin resistant (MIC $>$ 0.06) but cephalosporin sensitive then cefotaxime or ceftriaxone should be continued (AR)
    - If the pneumococcus is both penicillin and cephalosporin resistant, continue using 2 g ceftriaxone IV 12-hourly or 2 g cefotaxime IV 6-hourly plus vancomycin 15–20 mg/kg IV 12-hourly plus 600 mg rifampicin IV/orally 12-hourly (AR).
11. For patients with confirmed pneumococcal meningitis who have recovered by day 10 treatment should be stopped (1C).
12. For patients with confirmed pneumococcal meningitis who have not recovered by day 10, 14 days treatment should be given (1C)
13. For patients with penicillin or cephalosporin resistant pneumococcal meningitis, treatment should be continued for 14 days (1C)

Meningococcal meningitis

14. If *N. meningitidis* is identified:
    - Continue 2 g ceftriaxone IV 12 hourly or 2 g cefotaxime IV 6-hourly (AR)
    - 2.4 g benzylpenicillin IV 4-hourly may be given as an alternative (AR)
    - If the patient is not treated with ceftriaxone, a single dose of 500 mg ciprofloxacin orally should also be given (1C)
15. For patients with confirmed meningococcal meningitis who have recovered by day 5 treatment can be stopped (1C)

Other bacteria

16. If *Listeria monocytogenes* is identified:
    - Give 2 g ampicillin/amoxicillin IV 4-hourly (stop Ceftriaxone/Cefotaxime) and continue for at least 21 days (AR)
    - Co-trimoxazole 10–20 mg/kg in four divided doses(of the trimethoprim component) or

Table 6 Definitive antibiotic treatment.

Aetiology	Antibiotic (s)	Dose	Alternative antibiotic choices	Dose	Duration[b]
Neisseria meningitidis	Cefotaxime OR Ceftriaxone	2 g 6 hourly/2 g 12 hourly	Chloramphenicol (if anaphylaxis) OR Benzylpenicillin	25 mg/kg 6 hourly 2.4 g 4 hourly	5 days
Streptococcus pneumoniae (sensitivities unknown or penicillin resistant, cephalosporin sensitive)	Cefotaxime[a] OR Ceftriaxone[a]	2 g 6 hourly 2 g 12 hourly	Chloramphenicol	25 mg/kg 6 hourly	10 days (if stable) Up to 14 days if taking longer to respond
Streptococcus pneumoniae (penicillin sensitive, MIC $\leq$ 0.06)	Benzylpenicillin OR Cefotaxime OR Ceftriaxone[c]	2.4 g 4 hourly 2 g 6 hourly/2 g 12 hourly	Chloramphenicol	25 mg/kg 6 hourly	10 days (if stable) Up to 14 days if taking longer to respond
Streptococcus pneumoniae (penicillin and cephalosporin non-susceptible, penicillin MIC > 0.06 or cefotaxime/ ceftriaxone MIC > 0.5)	Cefotaxime OR Ceftriaxone AND Vancomycin[d] OR Rifampicin	2 g 6 hourly 2 g 12 hourly 15—20 mg/kg 12 hourly (adjusting according to serum trough levels) 600 mg bd	Chloramphenicol	25 mg/kg 6 hourly	14 days
Listeria monocytogenes	Amoxicillin	2 g 4 hourly	Co-trimoxazole	10—20 mg/kg (of the trimethoprim component) in 4 divided doses	21 days
Haemophilus influenzae	Cefotaxime OR Ceftriaxone	2 g 6 hourly 2 g 12 hourly	Moxifloxacin	400 mg od	10 days

[a] Add in IV Vancomycin 15—20 mg/kg bd or Rifampicin 600 mg bd if penicillin resistance is suspected e.g. patient has recently arrived from a country where penicillin resistant pneumococci is prevalent (if unsure, check with local infectious diseases/microbiology expertise.
[b] Treatment durations may need to be extended if patient is not responding.
[c] If low risk of *Clostridium difficile* infection and/or requiring outpatient therapy.
[d] Serum vancomycin trough concentrations of 15—20 ug/ml should be aimed for.

chloramphenicol 25 mg/kg 6 hourly are alternatives in cases of anaphylaxis to beta lactams (AR).

17. If *H. influenzae* is identified:
    - Continue 2 g ceftriaxone IV 12-hourly or 2 g cefotaxime IV 6-hourly for 10 days (1D)
18. If a member of the Enterobacteriaceae is isolated from blood or CSF:
    - Continue 2 g ceftriaxone IV 12-hourly or 2 g cefotaxime IV 6-hourly and seek specialist advice regarding local antimicrobial resistance patterns (AR)
    - If there is a high suspicion that an extended spectrum beta lactamase (ESBL) organism might be present IV Meropenem 2 g 8 hourly should be given (AR)
    - Treatment should continue for 21 days (AR)
19. In patients with no identified pathogen who have recovered by day 10 treatment can be discontinued (AR)

Patients with probable/confirmed meningococcal sepsis (no lumbar puncture):

20. Patients with confirmed meningococcal sepsis:
    - Continue 2 g IV ceftriaxone every 12 h or 2 g cefotaxime IV 6-hourly (AR)

- 2.4 g benzylpenicillin IV 4-hourly may be given as an alternative (AR)
- For patients who have recovered by day 5, treatment can be discontinued (1C).

21. For patients with a typical petechial/purpuric meningococcal rash but no identified pathogen who have been treated as above, and recovered by day 5, treatment can be stopped (1C).
22. In patients with confirmed or probable meningococcal sepsis who have not been treated with ceftriaxone, a single dose of 500 mg ciprofloxacin orally should also be given (1C)

All patients

23. Outpatient intravenous therapy should be considered in patients who are clinically well (AR)

Rationale

Definitive antibiotic choices are based on the organism identified (or likely organism) and its antimicrobial susceptibilities. As cephalosporins are recommended for empirical treatment, we recommend their continued use for patients found to have meningococcal or pneumococcal disease, although we recognise that some centres will prefer to narrow the spectrum and use benzylpenicillin for patients with a susceptible organism. Previously gentamicin has been advocated for its synergistic activities in listeria meningitis but its use is not supported by recent studies.[127,132] Vancomycin is recommended for penicillin resistance but it should never be used alone as there are doubts about its penetration into adult CSF, especially if dexamethasone has also been given.[133] A trough vancomycin level of 15–20 mg/L should be aimed for. It is widely accepted that this trough range should be aimed for in serious infection. Most of the evidence is in patients with staphylococcal infection and in patients with bacteraemia or pneumonia, but has been extrapolated to other infections.[134] Some experts also recommend repeating the lumbar puncture after 48–72 h of therapy in patients who have a penicillin and cephalosporin resistant pneumococcus. This should be discussed with an infection specialist on a case by case basis.

No beta-lactams other than ceftriaxone have been shown to reliably eradicate meningococcal carriage in the oropharynx. Therefore a single dose of Ciprofloxacin should be given to eliminate throat carriage to all patients in whom meningococcal disease is confirmed or strongly suspected, who have been treated with an antibiotic other than ceftriaxone (including those treated with cefotaxime). If ciprofloxacin is contraindicated rifampicin 600 mg twice daily for two days can be given as an alternative.

Meningitis caused by gram negative bacilli is rare, although incidence may be increasing.[7,135] In addition multidrug resistance such as extended spectrum beta lactamases (ESBLs) enterobacteriaciae is increasing. ESBL should be considered in patients who have Gram negative bacilli in the CSF or on blood culture **and** have recently returned from a country or area of high prevalence, or who have an ESBL cultured from other sites e.g. urine.

Duration of treatment

There is little evidence to guide the duration of treatment in adults. The recommendations here have been extrapolated from the paediatric literature. The duration of antibiotic therapy depends upon which pathogen is identified. The management of epidemic meningococcal meningitis in Africa with a single dose of ceftriaxone has been evaluated[52] and compared well with earlier studies of single doses of combined penicillins or depot chloramphenicol.[136] Short courses of penicillin (3 days) have been advocated for treatment of uncomplicated adult meningococcal meningitis in New Zealand but have not been evaluated in controlled, prospective studies.[137] A meta-analysis found no difference between short (4–7 days) versus long (7–14 days) courses of antibiotics for all causes of bacterial meningitis.[138] However, no trials in adults were identified for inclusion. In a subsequent double-blind randomised equivalence study conducted in Bangladesh, Egypt, Malawi, Pakistan, and Vietnam, it was concluded that antibiotics can be safely discontinued in children who are stable by day 5 of ceftriaxone treatment.[139]

We recommended that if the patient is judged clinically to have recovered by 10 days for pneumococcal disease and 5 days for meningococcal disease the antibiotics can be stopped. In addition, if no pathogen has been found antibiotics can be stopped after 10 days if the patient has clinically recovered.

Alternative antibiotic therapy approaches

Alternative antibiotics may be useful in cases of allergy, or increased antimicrobial resistance. Carbapenems have a broad range of activity against Gram-positive and Gram-negative bacteria. Controlled trials in children and a small number of adults, suggest that meropenem has similar efficacy to cefotaxime or ceftriaxone in the treatment of bacterial meningitis[140] and may be useful in the future. Gatifloxacin and moxifloxacin penetrate the CSF well and experimental models support their potential role in the treatment of penicillin and cephalosporin-resistant meningitis,[141,142] however there is concern regarding the rapid emergence of resistance with fluoroquinolone treatment.[143] Intraventricular antimicrobial agents have been shown to be of use in nosocomial meningitis associated with extra ventricular drains,[144]but are not indicated in the management of adult community acquired bacterial meningitis. There is some evidence from animal models of pneumococcal meningitis that compared with ceftriaxone, antibiotics such as daptomycin and rifampicin sterilise the CSF more rapidly, modulate CSF inflammation, and protect against cortical injury.[145,146] However, until there are human trials to support the use of these antibiotics they cannot be recommended as an alternative to cephalosporins.

Outpatient antibiotic therapy

Outpatient antibiotic therapy (OPAT) is increasingly being used for many different infections including meningitis.[147–150] Outpatient therapy has cost savings by freeing up hospital beds and there may be psychological benefits

Box 9. Outpatient therapy (OPAT) of meningitis and meningococcal disease.

7a. Indications where outpatient therapy may be appropriate
- The decision to commence OPAT must be made by a physician familiar with OPAT and should be carried out by a specialist OPAT team and include regular review of cases by a physician
- The patient should:
  - be afebrile and clinically improving
  - have received ≥5 days of inpatient therapy and monitoring (?shorter)
  - have reliable intravenous access
  - be able to access medical advice/care from the OPAT team or delegated individuals 24 h a day
  - have no other acute medical needs other than the need for parenteral antimicrobials
- The patient and family/carer must be willing to participate in OPAT

7b. Regimes that could be used in the community
- Ceftriaxone 2 g bd IV (4 g od IV can be used after the first 24 h of therapy)
- Ceftriaxone 2 g bd IV and Rifampicin 600 mg bd PO for penicillin resistant pneumococci

for the patient treated in their own home.[151,152] Some indications for when OPAT may be appropriate and what regimens might be considered are given in Box 9.

There is concern regarding once daily cephalosporins in meningitis and the risk of having sub-therapeutic levels. Animal studies have shown that once daily ceftriaxone achieves similar CSF sterilisation rates as twice daily after the first 24 h[153] and a small clinical study, with no comparator arm, showed once daily ceftriaxone achieved effective CSF concentrations and sterilised the CSF within 24–48 h.[154] In the first 24 h cephalosporins should be given twice a day to achieve rapid CSF sterilisation, thereafter they can be given once daily to patients who have recovered sufficiently to be considered for OPAT.

Which adjunctive treatment should be given?

Recommendations

For patients with suspected meningitis:

24. 10 mg dexamethasone IV 6 hourly should be started on admission, either shortly before or simultaneously with antibiotics [1A].
25. If antibiotics have already been commenced 10 mg IV dexamethasone every 6 h should still be initiated, up until 12 h after the first dose of antibiotics (AR).
26. If pneumococcal meningitis is confirmed, or thought probable based on clinical, epidemiological and CSF parameters, dexamethasone should be continued for 4 days [1C].
27. If another cause of meningitis is confirmed, or thought probable, the dexamethasone should be stopped (1C).
28. Glycerol is not recommended as adjuvant therapy for community acquired bacterial meningitis in adults [1B].
29. Therapeutic hypothermia is not recommended for adults with bacterial meningitis [1B]

Rationale

Over 10% of adults with bacterial meningitis die, even when appropriate antibiotics are started promptly, and it is likely that major further improvements in outcome will not come from changes in antibiotic therapy but from manipulation of the host responses to infection or with the development of alternatives to antibiotics, such as engineered liposomes — still in early animal trials.[155]

The role of corticosteroids in community acquired bacterial meningitis

Corticosteroids have many potential anti-inflammatory effects in bacterial meningitis including decreasing the amount of cytokines released, for example, through inhibiting the transcription of mRNA for TNF-α and IL-1[156–160] and inhibition of the production of prostaglandins and platelet activating factor.[161] Methylprednisolone decreases meningeal inflammation in a rabbit model of pneumococcal meningitis,[162] decreases CSF outflow resistance[163] and reduces cerebral oedema.[164] Dexamethasone plus ceftriaxone when given in a rabbit model of *H. influenzae* meningitis resulted in significantly reduced CSF TNF-α concentration and a reduced CSF white cell count.[160] In these animal models the improvement in outcome only occurred when dexamethasone was given before or with the antibiotics.[160]

On the other hand corticosteroids may be associated with side effects. In experimental models the administration of corticosteroids reduced the penetration of antibiotics into the CSF,[133] although this has not been born out in small studies conducted in humans.[165–167] Animal studies also suggest that corticosteroids can aggravate the cognitive deficits that may occur after bacterial meningitis.[168] Trials of corticosteroids in man have shown conflicting results regarding overall benefit. Controlled trials in children showed some benefit in reducing deafness and neurological deficit, largely in meningitis caused by *H. influenzae*. Dexamethasone, given before or with the first dose of antibiotics in adults, improved outcome, particularly in those with pneumococcal meningitis, in a Dutch trial.[169] In contrast, 20 years of experience in Croatia and randomised controlled trials of adult meningitis in Malawi and Vietnam did not show any benefits overall.[170–172] Two systematic reviews and one meta-analysis (including four studies from 1999 to 2007) suggested that adjunctive corticosteroids are beneficial in adults with bacterial meningitis in high-

income countries.[173–175] However, a subsequent meta-analysis of individual patient data from trials amongst children and adults in resource-rich and poor settings showed no benefit.[176] This analysis is confounded, however, by considerable heterogeneity between the trials analysed.

The most recent Cochrane review concluded there was a small reduction in mortality for patients with pneumococcal meningitis who received corticosteroid therapy, but not other causes. There was also a reduction in hearing loss and short term neurological sequelae for all causes.[173] Data from this review and a meta-analysis of individual patient data showed no difference in outcome when comparing corticosteroids that were given before or after antibiotics,[176] there was even a slight improvement in hearing loss in the studies that gave steroids post antibiotics.[173] The data so far do not show any increase in adverse events, such as increased cognitive deficits or gastrointestinal bleeding.[173,177,178] A potential rare complication of dexamethasone therapy in pneumococcal meningitis is delayed cerebral thrombosis[179,180] although a causal relationship between this complication and dexamethasone has not yet been established.

Given that there is no evidence for harm in giving corticosteroids, and that some groups do appear to benefit, we recommend that for adults in whom bacterial meningitis is suspected, dexamethasone be given before, or up to 12 h after, antibiotics are started. Steroids should be then stopped, if a cause, other than *Streptococcus pneumoniae* is identified. If no cause is found and pneumococcal meningitis remains most likely based on clinical, epidemiological and CSF parameters, the steroids should be continued for 4 days.

Whilst high dose steroids are used in meningitis to reduce brain inflammation and oedema, low dose hydrocortisone is occasionally used in septic shock to restore haemodynamic stability. Recommendations on when hydrocortisone would be appropriate in septic shock can be found below and in the surviving sepsis guidelines.[41]

Adjunctive therapy with glycerol in community acquired bacterial meningitis

Glycerol is a hyperosmolar agent that has been used to decrease intracranial pressure in a number of brain conditions. A randomised clinical trial in Finland suggested that glycerol might protect against sequelae in children with bacterial meningitis.[181] However, a subsequent South American trial showed no significant benefit of adjuvant intravenous dexamethasone, oral glycerol, or both on death or deafness but there was a reduction in neurological sequelae in both the glycerol alone group and those who received dexamethasone and glycerol.[182] Later randomised trials in Malawi found an increase in mortality in adults treated with glycerol and no benefit in children.[183,184]

Other therapeutic approaches

Animal models and individual patient data suggested a potential benefit of induced hypothermia in bacterial meningitis.[185,186] However a recent randomised controlled trial was stopped prematurely because of excess mortality in the hypothermia arm.[187]

Critical care

Which patients with suspected or confirmed meningitis should be referred for critical care?

Recommendations

1. Intensive care teams should be involved early in patients with rapidly evolving rash, evidence of limb ischaemia, cardiovascular instability, acid/base disturbance, hypoxia, respiratory compromise, frequent seizures or altered mental state (1B).
2. The following patients should be transferred to critical care (1B):
   a. Those with a rapidly evolving rash
   b. Those with a GCS of 12 or less (or a drop of >2 points)
   c. Those requiring monitoring or specific organ support
   d. Those with uncontrolled seizures
3. Intubation should be strongly considered in those with a GCS of less than 12 (AR)
4. Patients with evidence of severe sepsis should be managed in a critical care setting in accordance with the surviving sepsis guidelines (AR).

Rationale

Given the predisposition of patients with bacterial meningitis and meningococcal sepsis to deteriorate quickly, and the high mortality rate, critical care input should be sought early in patients with risk factors for a poor outcome, especially a reduced GCS, haemodynamic instability, persistent seizures, and hypoxia.[188] Patients with meningococcal sepsis are typically young adults, who tend to maintain their blood pressure until late in disease, and then deteriorate rapidly. Patients should be examined for other signs of cardiac instability and impaired perfusion for example delayed capillary refill time, and dusky or cold extremities.

What other critical care management issues are important?

Recommendations

5. Patients should be kept euvolaemic to maintain normal haemodynamic parameters (2C)
6. Fluid restriction in an attempt to reduce cerebral oedema is not recommended (2C)
7. When intravenous fluid therapy is required, crystalloids are the initial fluid of choice (1B)
8. Albumin should be considered in patients who have persistent hypotensive shock in spite of corrective measures (1C)
9. Patients with suspected or proven raised intracranial pressure should receive basic measures to control this and maintain cerebral perfusion pressure (1C)
10. Routine use of ICP monitoring is not recommended (AR)
11. Hydrocortisone (200 mg od) should also be considered in patients with persisting hypotensive shock (2C)

12. A mean arterial pressure (MAP) of >/= 65 mmHg is recommended; although this may need to be individualised (1B)
13. Use norepinephrine as opposed to epinephrine or vasopressin as the initial vasopressor for hypotension after euvolaemia is restored (1B)
14. Suspected or proven seizures should be treated early (1C).
15. Patients with suspected or proven status epilepticus (including non-convulsive/subtle motor status), such as those with fluctuating GCS off sedation or subtle abnormal movements, should have electroencephalogram monitoring (AR)

Evidence

Adult patients with bacterial meningitis and meningococcal sepsis have differing needs for intravenous fluid therapy. Some patients, such as those with primarily meningitis and little evidence of sepsis, are relatively euvolaemic, whereas others have profound or occult shock requiring early restoration of circulating volume. Over-vigorous administration of intravenous fluids in patients with meningitis may risk exacerbation of cerebral oedema, but paediatric meningitis studies have shown that fluid restriction may also contribute to a worse outcome.[189,190] Consequently, the management of meningitis should target the maintenance of a normal circulating volume avoiding both under and over-hydration and the associated adverse outcomes.

In patients with meningitis, control of raised intracranial pressure is also essential to prevent mortality although it is still not clear how best to achieve this and there is not sufficient evidence to support the routine use of ICP monitoring.[31,191] Measures such as achievement of normal to elevated MAP, control of venous pressure, head elevation, avoidance of hyperthermia and hyponatraemia and maintenance of normocarbia and normoglycaemia may be considered.[192]

Seizures have been reported to occur in 15% of patients with acute bacterial meningitis and are associated with a worse outcome,[9] therefore anticonvulsant treatment should be started promptly even when seizures are suspected but not proven.[193] Patients with suspected or proven status epilepticus should also have EEG monitoring.

The aim of fluid replacement in meningococcal sepsis is to reverse shock, as shown by normalisation of lactate levels and maintenance of urine output at >/=0.5 ml/kg/h. The type of fluid to be given, in all types of sepsis, has been debated but in general it seems that albumin does not have any survival benefit over crystalloids alone.[194]In a subgroup analysis of this study, albumin was associated with some improvement in survival and a shorter duration of vasopressors in those with more severe sepsis, where shock was also present. Albumin should be considered in patients with sepsis who have worsening shock and require significant amounts of fluid resuscitation.

Although the Waterhouse—Friderichsen syndrome with adrenal failure is very rare, there is some evidence that refractory septic shock may be more common in patients with impaired adrenal responsiveness.[195,196] Low-dose, steroid supplementation may improve survival in those with refractory septic shock and documented adrenal hypo responsiveness.[197] Hydrocortisone, at a dose of 200 mg once a day, should be given in cases of resistant shock.[41] A MAP of ≥65 mmHg is the target for most patients although this will need to be individualised in specific cases; in a younger patient with significant shock, dusky looking digits and minimal cerebral oedema, a lower MAP (such as 50—60 mmHg) may be acceptable, whereas, in an older patient with evidence of cerebral oedema a higher MAP (such as 70 mmHg), and hence cerebral perfusion pressure, may be desirable. Norepinephrine is the vasopressor of choice given that it has equivalent efficacy to dopamine but less adverse events.[198] Vasoactive agents such as norepinephrine should be initiated early in persistent shock, via a central vein. Dilute concentrations of these agents can be given through a peripheral vein until central access is established. A low-dose of glyceryl trinitrate (1—2 mg/h) may be useful in those patients with progressive shock and ischaemic digits.

Meningococcal sepsis is frequently associated with a procoagulant state, with the attendant risk of the development of microthrombi within the peripheral circulation. Over the last few decades it has been shown that these patients are often deficient in protein C, protein S, and antithrombin III,[199—201] have a defective endothelial protein C activation pathway[202] and have both low and dysfunctional platelets.[203—205] Patients with bleeding and overt DIC (indicated by low platelets, low fibrinogen and elevated clotting times) should be treated according to established management guidelines.[206] Blood products may also be used to correct anaemia, thrombocytopenia and coagulopathy in consultation with local haematology teams.

Prevention

What measures should be taken to prevent secondary cases?

Recommendations

1. All cases of meningitis (regardless of aetiology) should be notified to the relevant public health authority (AR).
2. The Consultant in Communicable Disease Control (CCDC) or Consultant in health protection in the Public Health England health protection team should be contacted early (AR).
3. Prophylaxis of contacts should be initiated by the CCDC/Consultant in health protection and not the admitting clinicians (AR).

Rationale

Meningitis and meningococcal sepsis are notifiable diseases in the UK.[207—209] There is a legal obligation to ensure the relevant public health authority is aware of all cases. Any prophylaxis of contacts should be instigated by the public health team, although in some instances the clinical team may be asked to arrange the prescription.[210]

Meningococcal infection
Recommendations

4. Ciprofloxacin should be given to all close contacts of probable or confirmed meningococcal meningitis (1C)
   - 500 mg stat for adult contacts
   - 250 mg stat for child contacts aged 5—12 years
   - 30 mg/kg up to a maximum of 125 mg stat for child contacts under 5 years
5. In those unable to take Ciprofloxacin, Rifampicin can be given as an alternative (1C).
   - 600 mg twice a day for 2 days for contacts over the age of 12
   - 10 mg/kg twice a day for 2 days for contacts aged 1—12 years
   - 5 mg/kg twice a day for 2 days for contacts aged less than 12 months
6. Vaccine can be given to any unvaccinated contacts of cases caused by any non-B serogroup(1C)
7. If 2 or more cases of serogroup B disease occur within the same family vaccination against serogroup B should be offered to all household contacts (AR)

In addition to prophylaxis to contacts the following should also be offered to the index case:

8. Any unimmunised index case under the age of 25 years (whatever the capsular serogroup) should be offered vaccination according to the national schedule (currently monovalent MenC at 3 months, combined Hib/MenC at 12 months and MenACWY vaccine at 13/14 years) (1D)
9. Cases of confirmed serogroup C disease who are eligible for vaccination and have previously been immunised with Meningococcal C conjugate (or polysaccharide) vaccines should be offered a booster dose of Meningococcal C conjugate vaccine around the time of discharge from hospital (1D)
10. If two or more cases of probable/confirmed IMD due to the same vaccine preventable strain in the same educational or residential setting within a four week period occur then wider vaccination may be offered in line with national guidance[211] (AR)

Rationale
Although 10% of the population may carry meningococci asymptomatically at anyone time, carriage rates are age dependent. Less than 2% of children aged under 5 years and 20—25% of older teenagers and young adults carry the meningococcus.[212] Secondary attack rates are approximately 2—4 per 1000 population in close contacts of cases; a 1000-fold increase above the overall reported attack rate of meningococcal disease in adults (0.23/100,000).

Most patients with systemic disease have acquired the invading meningococcus within the previous 7 days and secondary prevention targets household contacts within the previous week. Other close contacts would include 'intimate kissing contacts'. For antibiotic prophylaxis, the use of single dose ciprofloxacin is now recommended in preference to rifampicin in all age groups and in pregnancy, particularly because it is a single dose and is readily available in high street pharmacies. Ceftriaxone as a single dose or Rifampicin given over two days are alternatives.[210]

Regardless of the use of prophylaxis an extra risk persists for at least 6 months in contacts of patients with invasive infection. The general practice records of all close contacts of meningococcal disease should be labelled to alert doctors that an increased risk of meningococcal disease persists for 6 months. Contacts of cases of disease caused by vaccine preventable non-B serogroups should be offered vaccination.[213]

After a *second* confirmed serogroup B case occurs in a household, meningococcal serogroup B vaccination (Bexsero®) should be considered in addition to chemoprophylaxis for all household contacts, even if the interval between the two cases is >30 days and/or the serogroup B strains are subsequently identified to be different.[214]

***H. influenzae* type b infection**
Recommendations

1. Where *H. influenzae* type B is confirmed as the cause the index case and all household contacts, in households which contain an at risk individual, should receive prophylactic Rifampicin (20 mg/kg to a maximum of 600 mg, once daily for 4 days), this should normally by initiated by the appropriate health protection team following notification (1C)
2. Vaccination should be given to all previously unvaccinated household contacts, under the age of 10 (1C)

Rationale
H. influenzae meningitis is uncommon in adults but if infection is caused by a type b strain then it should be confirmed that all children aged up to 10 years among household contacts have received *H. influenzae* type b (Hib) vaccination; household contacts are defined as any individual who has had prolonged close contact with the index case in a household-type setting during the seven days before the onset of illness. Children younger than 10 years who have never been immunised against Hib should receive vaccination according to recommendations given in the 'green book'.[213] In a household where there is an at risk individual (a child under 10 or a vulnerable individual of any age such as the immunosuppressed) all household contacts and the index case should be given rifampicin 20 mg/kg once a day (maximum of 600 mg) for 4 days for adults and children older than 3 months. Infants younger than 3 months should receive 10 mg/kg once a day for 4 days.

Pneumococcal meningitis
Close contacts of pneumococcal meningitis are not usually at an increased risk of pneumococcal infection and antibiotic prophylaxis is not indicated. Clusters of invasive pneumococcal disease occurring in elderly care homes, for example, should be discussed with local health protection authority.

Screening for predisposing factors to meningitis or meningococcal sepsis
Recommendations

3. All patients with meningitis should have an HIV test (1C)
4. Patients with a single episode of meningitis or meningococcal sepsis should not be screened for any other

immunological deficiency unless there was some other indication (1C)
5. All patients with two or more episodes of meningococcal or pneumococcal meningitis should have appropriate immunological investigations (1B)
6. All patients who have a family history of more than one episode of meningococcal disease should have appropriate immunological studies (1C)
7. Patients with either a history of trauma or recent neurosurgery or evidence of rhinorrhea or otorrhoea should have investigations for a CSF leak (AR).

Rationale

HIV and meningitis

HIV can cause meningitis either directly or indirectly via opportunistic infections. Meningitis caused by HIV itself most often occurs during acute HIV infection but can occur in established infection.[215–217] Up to 24% of patients with acute HIV infection may present with meningitis as part of a seroconversion illness.[218–220] Headache and fever are common and there are often also other symptoms or signs such as lymphadenopathy, oral candidiasis or rash.[215,221] The prevalence of HIV in culture negative meningitis has been reported between 1 and 5% in German and US cohorts.[19,222] Pneumococcal and meningococcal meningitis have both been reported to have a higher incidence and a higher mortality in HIV positive than HIV negative patients.[217,223] HIV should therefore also be included in the differential diagnosis in all cases of meningitis.[224] During the early phase of seroconversion illness, HIV antibody tests may be negative. Many centres now have combined assays for HIV antibody and p24 antigen (4th generation assays). If there is a strong suspicion but the test is negative then consider performing an HIV RNA PCR.

If a patient lacks capacity to consent and in the absence of a power of attorney or advance directive, an HIV test should be performed if it is deemed to be in the patient's best interests (England and Wales) or of benefit to the patient (Scotland). Further information can be found in the British HIV Association guidance on HIV testing.[225]

Other predisposing conditions

Any case of pneumococcal meningitis (confirmed or probable) should prompt a review of the patient's medical history to establish whether they are in a recognised risk group[213] and whether they have been appropriately immunised. Adults with asplenia or splenic dysfunction may be at increased risk of invasive pneumococcal infection. Such individuals, irrespective of age or interval from splenectomy, may have a sub-optimal response to the vaccine. Adults with complement deficiency, or on Eculizumab (Soliris) therapy, are at increased risk of invasive meningococcal infection, and as such should be vaccinated and take prophylactic antibiotics. A clinical immunologist should determine what investigations would be appropriate in cases of recurrent meningitis or in cases where there is a family history of meningococcal disease.

A CSF leak due to disruption of the meninges, which may be spontaneous, traumatic or iatrogenic, is a rare cause of bacterial meningitis and may be recurrent. In patients with recognised features such as rhinorrhoea or otorrhoea or risk factors such as trauma or neurosurgery, investigations to identify the source of leak, including CT and/or MRI are warranted.[226,227]

What are the appropriate infection control measures?

Recommendations

8. All patients with suspected meningitis or meningococcal sepsis should be respiratory isolated and until meningococcal meningitis or sepsis is excluded, or thought unlikely, or they have received 24 h of Ceftriaxone or a single dose of Ciprofloxacin (1C)
9. All patients with confirmed meningococcal meningitis or meningococcal sepsis should be isolated and barrier nursed until they have received 24 h of IV Ceftriaxone or had a single dose of oral ciprofloxacin (or 48 h of Rifampicin) (1C)
10. Droplet precautions should be taken until a patient has had 24 h of antibiotics. This includes the wearing of surgical masks if likely to be in close contact with respiratory secretions or droplets (2C)
11. Antibiotic chemoprophylaxis should be given to healthcare workers who have been in close contact with a patient with confirmed meningococcal disease ONLY when exposed to their respiratory secretions or droplets for example during intubation or as part of CPR when a mask was not worn (1C)

Other causes of meningitis do not require isolation

Rationale

Suspected meningitis is one of the commonest occupational exposures for healthcare workers,[228] although healthcare associated infection is extremely rare.[229] The estimated risk is 25 times greater than that of the general population although lower than that of household contacts.[229] Droplet precautions are recommended until a patient has had 24 h of effective antibiotic therapy. These precautions include nursing the patient in a single room, surgical masks to be worn by all if in close contact (<3 feet) with the patient, and other standard infection prevention precautions.[230] Antibiotic prophylaxis is only required for those whose mouth or nose has come into close contact with the patients respiratory secretions. This is likely to be those who are involved in airway management without wearing a mask.

Follow up and sequelae

What follow up should be arranged and what sequelae should be considered?

Recommendations

1. All patients should be assessed for potential long-term sequelae, both physical and psychological before discharge from hospital (AR).
2. The following sequelae should documented if present (AR):

- Overt hearing loss and/or problems with balance, dizziness and tinnitus
- Other neurological injury resulting in
  - cognitive deficits and learning impairment
  - epilepsy
  - movement disorders
  - visual disturbances
  - other communication problems
- wounds, tissue damage and skin scars
- amputations and other orthopaedic sequelae
- psychiatric and psycho-social problems
- renal impairment

3. For patients receiving treatment in a critical care setting at any point in their illness, assessment and rehabilitation should conform to the NICE guidelines on rehabilitation after critical illness (AR)
4. Hearing tests
   a. Patients (including those who have had meningococcal sepsis) should have a hearing test if the clinician, the patient or their family thinks hearing may have been affected, or if the patient no longer has the capacity to report hearing loss (AR).
   b. The hearing test should take place before discharge or within 4 weeks of being well enough to test, whichever is sooner (AR).
   c. The hearing test should be carried out by a hospital based specialist (AR).
   d. Patients found to have severe to profound deafness should be offered a 'fast-track' assessment for cochlear implant (AR).
5. All patients with confirmed or probable bacterial meningitis should be given a medical follow up appointment within 6 weeks after discharge (AR).
6. For patients with rehabilitation needs a rehabilitation plan should be agreed with the patient, and their family/carers (AR)
7. All patients and their families should be provided with the contact details of support organisations such as the Meningitis Research Foundation (www.meningitis.org) or Meningitis Now (www.meningitisnow.org) (AR).

Rationale

Bacterial meningitis and meningococcal disease can cause a variety of disabling sequelae resulting from either direct neurological injury, or from damage secondary to sepsis. Sequelae are more common following pneumococcal meningitis, and occur in about 30% of such patients compared to 7% with meningococcal meningitis.[9,231] The frequency of sequelae is much higher in meningococcal sepsis (up to 57%).[232,233] Some sequelae only become apparent after the acute phase of the illness.[177,234] Physical and psychological sequelae can have profound effects on both the patient and their family.[235] Some of the more urgent complications are shown in Box 10.

A prompt hearing assessment is essential in any patient reporting hearing loss. Cochlear ossification can progress rapidly and if not picked up early the success of cochlear implant surgery is jeopardised. This problem has been well described in children[236] but also occurs in adults.[237] Although initial hearing loss may subsequently recover post-meningitis, this should not delay a timely audiological review in the first instance. If a test is carried out early on and the result shows hearing within the normal range, then no further tests would be indicated. However, if the first test shows a hearing loss, this would be followed up by subsequent tests to review the situation after a period of time.

Neurological damage can be severe and plainly evident, or may result in more subtle cognitive sequelae.[177] The injury can cause deficits in many different domains. Where there is concern, patients should have access to neuropsychological and neurological assessment,[238] which can help

Box 10. Complications of acute meningitis and meningococcal sepsis.

	Complication	Warning signs	Action
Meningitis	Subdural empyema	Persistent fever New neurology	Urgent imaging WITH contrast Neurosurgical opinion
	Seizures (generalised tonic-clonic or subtle motor)	Abnormal movements Reduced consciousness	EEG monitoring
	Hydrocephalus	Reduced consciousness	Neuroimaging and neurosurgical opinion
	Cerebral venous sinus thrombosis	Reduced consciousness New focal neurological signs Failure to improve	MR venogram
Meningococcal Sepsis	Purpura fulminans	Rapidly progressive rash	Ensure on appropriate antibiotics Involve critical care and infection specialist as soon as possible
	Septic shock	Cold peripheries Refractory hypotension	Ensure on appropriate antibiotic therapy Involve critical care and infection specialist as soon as possible

EEG — Electroencephalogram; MR — Magnetic resonance.

detect subtle impairment and may facilitate functional recovery.

Life-altering sequelae, or prolonged hospitalisation can have profound psychological impacts, as described in the NICE guidelines, 'Rehabilitation after Critical Illness'.[239] Emotional and psychological difficulties are well documented after acquired brain injury.[240] Clinicians should consider the need for early referral to mental health services. Scarring and amputation due to meningococcal sepsis creates particular problems with adjustment to altered appearance,[241,242] and early psychological assessment and treatment are beneficial.[243]

Longer term, meningitis and sepsis can result in arthritis, limb pain, muscle pain and neuropathic pain. Headaches are frequently reported, occurring in up to one third of patients.[244]

In the UK, the support, information and advocacy provided by support organisations such as the Meningitis Research Foundation (www.meningitis.org) or Meningitis Now (www.meningitisnow.org) can provide crucial help with this.

Many patients feel well at discharge from hospital and do not realise that they may not be able to return to all their normal duties and activities immediately. Fatigue, sleep disorders, and emotional difficulties are frequently reported in the weeks and months after discharge.[245] Support from hospital clinicians and GPs can help with this and enable patients to stage their return to work or studies on a part-time basis initially.

Follow-up care is important, and several studies have shown that it is not routinely offered where it is needed. In a study of adolescents with meningococcal disease,[233] only half were offered any post-discharge follow up care. Post-hospital follow up should be offered to all with confirmed or probable bacterial meningitis because many issues will only become apparent after discharge.

Viral meningitis

Recommendations

1. If viral meningitis is suspected on clinical, epidemiological and CSF grounds:
   - the CSF should be tested for enteroviruses, herpes simplex viruses type 1 and 2 (HSV-1 and HSV-2) and varicella zoster virus (VZV) by PCR (1C)
   - PCR testing of CSF, or serological assays, for other viruses should be guided by additional features in the history and examination, e.g. immune compromise and travel history (1C)
   - Stool and/or throat swabs should be tested for enterovirus by PCR (1C)
2. Aciclovir/Valaciclovir should not be given as prophylaxis for recurrent herpes meningitis (HSV or VZV) (2B)

Background and rationale

Since the first edition of these guidelines (1999) the relative importance of viral meningitis has grown. This has been in part due to the reduction in bacterial meningitis[5,129] and in part due to the increased frequency with which viral meningitis is diagnosed, following more widespread use of molecular diagnostic technologies.[246]

Viral meningitis is often considered to be a self-limiting, benign illness[247,248] and although it is rarely fatal in immunocompetent adults, it can cause significant morbidity, and may be responsible for underappreciated sequelae.[245,249,250] Viral meningitis is characterised by inflammation of the meninges, in contrast viral encephalitis is infection and inflammation of the brain parenchyma itself. Encephalitis is associated with different pathogens and has a considerably worse prognosis.[251,252] It is characterised by changed behaviour, confusion or coma as opposed to headache and neck stiffness —the predominant features in viral meningitis. There are recently published guidelines on the management of viral encephalitis[64,253] and although viral meningitis and encephalitis may be differentiated clinically, if there is doubt, patients should be managed as suspected encephalitis. In addition, distinguishing viral meningitis from bacterial meningitis is crucial because of the different treatment, and outcomes.[15,254]

Epidemiology

The precise incidence of viral meningitis, particularly in adults, is unknown but is estimated to account for at least 50% of the total meningitis burden and possibly up to 80%.[8,15,27,255] As with bacterial meningitis it is probably under-diagnosed and under-reported.[256] In the UK, the commonest viruses that cause meningitis are the enteroviruses and the herpes viruses (predominantly HSV-2 and VZV). There are over 90 enterovirus serotypes and it is transmitted via the faecal-oral route. HSV-2 is a sexually transmitted disease and VZV is transmitted primarily via the respiratory route. Both VZV and HSV-2 meningitis can occur with primary infection or as reactivation of disease.

Other less common aetiologies include cytomegalovirus, Epstein—Barr virus and mumps virus — all of which should be considered if initial tests do not reveal a cause. HSV-1 is more commonly associated with encephalitis than meningitis.[18]

Clinical features

Patients with viral meningitis present with meningism (neck stiffness, headache and photophobia). Fever is not always present. Other non-specific symptoms such as diarrhoea, vomiting, muscle pain, and sore throat are sometimes seen.[257] Patients with HSV-2 meningitis rarely have concurrent genital ulcers caused by the virus and often don't have any history of genital disease. VZV meningitis can occur with or without the rash of chickenpox or shingles. There is usually no reduced conscious level in adults with viral meningitis. An alteration in conscious level suggests an alternative diagnosis such as bacterial meningitis, encephalitis, encephalopathy due to infection outside the central nervous system or other intracranial pathology such as a subarachnoid haemorrhage or a space occupying lesion.

How should viral meningitis be investigated?

Because the presenting clinical features for bacterial and viral meningitis are similar,[82] the initial investigations are the same, as described earlier in the investigations section.

If a viral cause is suspected following CSF examination (see Table 4) then viral pathogens should be looked for, normally by CSF PCR. Although a positive PCR may not lead to any specific antiviral treatment, identifying a viral pathogen allows the patient to be given a diagnosis and antibiotics to be stopped; it also reduces the number of investigations performed and the duration of hospital stay.[8,258,259]

CSF PCR is the gold standard for confirmation of viral meningitis.[246,260] Most laboratories will test for enterovirus, HSV-1, HSV-2 and VZV. No cause is found in 30—50% of patients with presumed viral meningitis.[18,19,254]

Other investigations

Unlike in bacterial meningitis the white cell count in the blood and CRP are often normal in viral meningitis (especially in herpes meningitis). In enteroviral meningitis, virus may also be detected by throat swabs, in stool, or skin vesicles if present.[261,262]

How should viral meningitis be treated?

There are currently no treatments of proven benefit for most causes of viral meningitis. Some clinicians treat herpes meningitis with aciclovir or valaciclovir, but to date, there is no evidence to support this, for either HSV or VZV. Although in theory these drugs may be beneficial, there are potential risks from drug side effects and unnecessarily prolonged hospitalisation; these risks should be weighed against the lack of evidence for efficacy. Treatment should be supportive with analgesia and fluids if necessary. If antibiotics have been commenced they should be stopped once a viral diagnosis is made, and priority given to expediting discharge from hospital. If there are any suggestions of encephalitis such as changes in personality, behaviour or cognition or altered conscious level intravenous aciclovir should be given for suspected HSV encephalitis, and the British Infection Association/Association of British Neurologists guidelines on the management of encephalitis should be followed.[64]

Some people suffer from recurrent episodes of lymphocytic meningitis or, as it is often referred to eponymously, Mollaret's meningitis.[263] Large granular plasma cells are considered to be the hallmark of Mollaret's meningitis, but in reality, these are rarely seen. Recurrent lymphocytic meningitis is most often caused by HSV-2,[264—266] although there have been case reports of other viruses.[267—270] The episodes of meningitis can be months to years apart but there is normally complete recovery in between episodes. Despite oral valaciclovir reducing transmission of genital HSV-2 between discordant couples[271] and reducing recurrences in genital disease[272] it did not reduce recurrent HSV-2 meningitis in a placebo-controlled trial; indeed patients who received valaciclovir tended to have a greater rate of relapse once the trial stopped.[273] The lack of efficacy was postulated by the authors to be due to low levels of drug in the CSF (although aciclovir concentration was not measured in this study). Potentially a higher dose may give better outcomes but no study has evaluated this as yet. Patients with recurrent episodes of confirmed or probable viral meningitis should be assessed by an infection or neurological specialist.

When should these guidelines be reviewed?

These guidelines and the relevant literature will be reviewed at 5 years after publication. If anything significant is published in the interim there will be an interim guideline statement issued.

Author contributions

FM performed initial literature search; FM,BDM and SD finalised literature that addressed the key questions; SD and NB wrote audit tool; FM,RH,LG,BM,SD,RR and TS developed the algorithm; FM wrote the initial drafts; all authors contributed to individual sections; FM,RH,RR and TS edited the final drafts; all authors reviewed the final manuscript.

Conflict of interest statement

Dr. Wyncoll reports personal fees from Sage Products, personal fees from Pfizer, personal fees from Johnson & Johnson, personal fees from Astellas, personal fees from Vygon, personal fees from Fisher and Paykel, outside the submitted work. All other authors report no conflicts of interest.

Acknowledgements

The working party would like to acknowledge the following people for their assistance with these guidelines. Dr Huw Cooper, Professor C H Raine and William Brassington gave advice regarding audiological follow up post-meningitis. The authors would also like to acknowledge all who contributed through the consultation period. The British Infection Association and the Meningitis Research Foundation funded a meeting to discuss the recommendations. FM is an NIHR doctoral research fellow. BDM is an NIHR Academic Lecturer. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, the Department of Health or Public Health England. This work was conducted independently of influence from the NIHR.

Appendix A. Supplementary data

Supplementary data related to this article including an audit tool and a copy of the updated algorithm, can be found at http://dx.doi.org/10.1016/j.jinf.2016.01.007.

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