Management of acute meningitis

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Acute meningitis remains a devastating disease. Clinicians need a low threshold for suspecting meningitis, to undertake appropriate investigations and provide treatment in a timely manner, to minimise the risk of poor outcome in bacterial disease, while limiting unnecessary treatment in viral meningitis.

Definitions
Meningitis is inflammation of the meninges covering the brain. It is a pathological definition. The cerebrospinal fluid (CSF) typically exhibits an elevated number of leucocytes (or a pleocytosis). In adults, >5 leucocytes/μL is defined as elevated. Bacterial or viral meningitis is confirmed by the detection of a pathogen in the CSF. Bacterial meningitis may also be suggested by symptoms of meningism and appropriate bacteria in the blood. 1

Causes
The most common causes of meningitis in immunocompetent adults in the UK are viruses and bacteria. Viruses account for up to half of cases. Enterovirus is the commonest, with herpes simplex and varicella zoster the next most frequent. Streptococcus pneumoniae and Neisseria meningitidis are the commonest bacteria, together accounting for approximately one-quarter of cases. Other causes such as Haemophilus influenzae, Listeria monocytogenes, Mycobacterium tuberculosis and fungi (typically cryptococci) are less frequently detected, together representing <10% of cases. Currently, many adults with meningitis have no pathogen detected. 2-5

Although this article refers to Listeria and tuberculous meningitis, it purposely focuses on the more common causes, ie viral and bacterial meningitis.

Clinical features
Clinical features alone cannot confirm the diagnosis of meningitis. A lumbar puncture (LP) is essential to confirm the diagnosis of meningitis and establish the cause.

In one study, 95% of bacterial meningitis patients had at least two symptoms of headache, neck stiffness, fever and altered consciousness. The latter three features were present together in only 44% of cases. Neurological deficits are found in around one-third of patients. 6 Similar findings are reported by other studies. 7-9 A rash in suspected meningitis makes N meningitidis more likely. However, 37% of meningococcal meningitis patients have no rash. 8 Varicella and enterovirus can also be associated with a rash. Risk factors for Listeria meningitis include overt or relative immune compromise, the latter including chronic illness, diabetes, alcohol dependency, malignancy or old age. Listeria

Viral meningitis is the most common form of meningitis in the UK, but bacterial meningitis continues to be important, with a high mortality.

Clinical features are poor discriminators for meningitis, so urgent investigations, starting with lumbar puncture, are key.

Most patients do not need brain imaging before lumbar puncture. Patients exhibiting clinical features of brain shift warrant urgent CT. Otherwise, imaging can cause delays in commencing antibiotics, which can lead to increased mortality.

Aim to take 10 mL of CSF during LP. Larger volumes are especially useful to diagnose tuberculous meningitis, and enable additional aliquots to be available for further diagnostic testing.

Prompt testing of CSF and blood by PCR can hasten pathogen diagnosis and improve patient management.

Key points

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KEYWORDS: clinical, viral, bacterial, meningitis, management, diagnostics
Another person with meningitis, sepsis or tuberculosis are other useful diagnostic clues.

**Investigations**

**Lumbar puncture**

Lumbar puncture is the key investigation. It enables rapid confirmation of meningitis and type of infecting organism. Diagnostic yield of LP can be diminished by collecting small CSF volumes. At least 10 mL can be safely removed.\(^{1,12}\)

**Cerebrospinal fluid cell count**

Cerebrospinal fluid remains one of the most rapidly informative tests. Pleocytosis indicates meningeal inflammation, of which infection is the most common cause. Van de Beek and colleagues reported that >90% of adults with bacterial meningitis had a CSF leukocyte count >100 cells/μL.\(^4\) Absence of pleocytosis makes meningitis much less likely, but does not completely rule it out. Approximately 1–2% of patients with bacterial meningitis will have a normal CSF leukocyte count. Positive pathogen detection and an absence of pleocytosis more frequently occurs among children, the immunocompromised, those pretreated with antibiotics or with mycobacteria tuberculosis infection.\(^1\)

**Cerebrospinal fluid leukocyte differential**

Cerebrospinal fluid leukocyte differential can help predict which type of pathogen is causing infection. Lymphocyte predominance suggests viral, while neutrophil predominance suggests bacterial infection. There are several exceptions to this general guide, including CSF neutrophil predominance observed in association with tuberculous meningitis (Table 1).

**Cerebrospinal fluid biochemistry**

Cerebrospinal fluid glucose is normally approximately two-thirds the blood (plasma) concentration. It is often lower in bacterial and tuberculous meningitis. As CSF glucose is influenced by the plasma glucose, it is essential to measure blood glucose at LP, to obtain an accurate CSF: blood glucose ratio. A CSF: blood glucose ratio <0.36 is an accurate (93%) marker for distinguishing bacterial from viral meningitis.\(^1\)

Cerebrospinal fluid protein is normally <0.4 g/L. Elevated protein suggests inflammation. A CSF protein >0.6 g/L largely rules out bacterial infection.\(^1\)

**Cerebrospinal fluid parameters**

Cerebrospinal fluid parameters have been combined into tools to help diagnose bacterial meningitis. One prediction rule accurately distinguished bacterial from viral meningitis in two adult patient populations using retrospective data (area under the curve 0.97).\(^{14,15}\) Clinical prediction tools (using CSF, laboratory and clinical parameters) have also exhibited high accuracy when tested retrospectively in large child populations.\(^16\) No tools have been validated prospectively in adults in the UK.

**Pathogen detection**

Cerebrospinal fluid microscopy with Gram stain

Cerebrospinal fluid microscopy with Gram stain (or an acid fast stain for M tuberculosis) can rapidly detect bacteria. It has a sensitivity between 50% and 99%.\(^7\) Detection, particularly for M tuberculosis, is enhanced by collection of >10 mL of CSF and subsequent cytopsin.\(^11\)

Cerebrospinal fluid culture

Cerebrospinal fluid culture is historically regarded as the ‘gold standard’ for the diagnosis of bacterial meningitis. It is diagnostic in 70–85% of cases prior to antibiotic exposure. Sensitivity decreases by 20% following antibiotic pretreatment. Cerebrospinal fluid sterilization can occur within 2–4 hours of antibiotic administration for meningococci and pneumococci respectively.\(^11\) Lumbar puncture should be performed as soon as possible to maximise pathogen detection.

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**Table 1. Classical cerebrospinal fluid features for different causes of meningitis**\(^a\)

|                        | Normal          | Bacterial                | Viral               | Tuberculous     | Fungal            |
|------------------------|-----------------|--------------------------|---------------------|-----------------|------------------|
| Opening pressure (cm CSF) | 12–20          | Raised                   | Normal / mildly raised | Raised          | Raised           |
| Appearance             | Clear           | Purulent, turbid, cloudy | Clear               | Clear or cloudy | Clear or cloudy  |
| CSF WBC (cells/μL)     | <5              | Raised (>100)\(^b\)      | Raised (5–1000)\(^b\)| Raised (5–100)\(^b\) | Raised (5–100)\(^b\) |
| Predominant cell       | Neutrophils\(^c\) | Raised                  | Lymphocytes\(^d\)   | Lymphocytes\(^a\) | Lymphocytes       |
| CSF protein (g/L)      | Raised          | Mildly raised            | Markedly raised     | Markedly raised | Raised           |
| CSF plasma glucose ratio | >0.66          | Very low                 | Normal / slightly low | Very low        | Low              |
| CSF glucose (mmol)     | 2.6–4.5         | Very low                 | Normal / slightly low | Very low        | Low              |

Note: Local laboratory ranges for biochemical tests should be consulted. They may vary from the quoted values here. A traumatic lumbar puncture (LP) will affect the results by falsely elevating the white cells due to excessive red cells. A common correction factor used is 1:1000.

\(^a\)Derived from Tom Salomon-Lecture Notes in Neurology

\(^b\)Occasionally the CSF white cell count (WCC) may be very high (several thousand) in bacterial meningitis. Alternatively the CSF WCC may be normal (especially in immunodeficiency or tuberculous meningitis).

\(^c\)May be lymphocytic if antibiotics given before LP (partially treated bacterial meningitis), or with certain bacteria, eg Enterococcus faecium.

\(^d\)May be neutrophilic in enteroviral meningitis (especially early in disease).

\(^a\)May be neutrophilic early in the disease course.

\(^a\)CSF = cerebrospinal fluid; WBC = white blood cell count; WCC = white cell count.
Cerebrospinal fluid polymerase chain reaction

Cerebrospinal fluid polymerase chain reaction (PCR), using pathogen specific nucleic acid sequences, can detect both bacteria and viruses with high sensitivity. Polymerase chain reaction is the ‘gold standard’ for diagnosis of viral meningitis. Polymerase chain reaction is increasingly relied upon in bacterial meningitis. It has far greater sensitivity than culture in invasive meningococcal disease. Cerebrospinal fluid PCR is particularly valuable in patients who receive antibiotics before LP. Polymerase chain reaction for 16S ribosomal RNA (present in almost all bacteria) enables a broad screen for bacteria, but has lower sensitivity than pathogen specific PCR.

Blood tests

Blood cultures should always be taken on admission and are helpful when antibiotics are started before LP. Blood cultures are positive in 50–80% of bacterial meningitis cases. Blood PCR is increasingly important, especially as PCR detects bacteria several days after antibiotic initiation. Blood PCR substantially increases the confirmation in meningococcal disease. Despite these tests, many patients will not have a cause identified for their meningitis.

Blood biomarkers, such as procalcitonin and C-reactive protein, can help distinguish bacterial from viral meningitis in adults and can be used to help guide treatment if no aetiology is found. C-reactive protein, C-reactive protein, procalcitonin and neutrophil gelatinase-associated lipocalin are all biomarkers for detecting bacterial meningitis, but none have far greater sensitivity than culture in invasive meningococcal disease. There is insufficient evidence to recommend their routine use in the NHS.

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Swabs

Throat, nasopharyngeal, and stool swabs are useful for detecting enteroviruses if the CSF PCR is negative.

Brain imaging

Brain imaging is neither obligatory in the management of meningitis, nor a prerequisite to LP. Performing neuroimaging before LP is associated with delays in commencing antibiotics, which in turn can lead to an increase in mortality. An urgent CT scan should be performed if there are clinical signs of brain shift. Clinical features indicative of a brain shift include focal neurological signs and reduced Glasgow Coma Score (GCS) (Box 1). The 2016 UK meningitis guidelines recommend an LP be performed without prior neuroimaging if the GCS is ≤12.

Patients with a GCS ≤12 should be considered for critical care assessment and neuroimaging. Imaging, particularly when contrast is used, may exhibit meningeal enhancement in meningitis. When brain shift is identified liaison with critical care and neurosurgical teams are essential.

A summary of investigations is presented in Fig 1.

Box 1. Indications for brain imaging before lumbar puncture (LP) in suspected meningitis

| Indications for brain imaging before LP in suspected meningitis |
|---------------------------------------------------------------|
| > Focal neurological signs                                    |
| > Presence of papilloedema                                    |
| > Continuous or uncontrolled seizures GCS12                   |

To exclude significant brain swelling or 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. Lumbar puncture without prior neuroimaging may be safe at levels below this.

GCS = Glasgow Coma Score

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Patient with suspected meningitis

**Bloods**
- Blood cultures
- Full blood count, urea, creatinine, electrolytes, liver function tests and clotting screen
- Procalcitonin or CRP
- Meningococcal and pneumococcal PCR
- Serology sample
- Glucose (pair with CSF glucose)
- HIV Ab/Ag test

**CSF**
- **No signs of sepsis or shock**
  - Opening pressure
  - Microscopy, culture and sensitivity
  - Glucose (pair with plasma glucose)
  - Protein
  - If **bacterial meningitis** seems likely based on CSF (WBC, Diff, Prot, Glu Ratio)
  - PCR for meningococcal and pneumococcal
  - If **viral meningitis** seems likely:
    - PCR for enterovirus, HSV 1, HSV 2, and VZV

**Further tests**
(If no aetiology identified on above tests)
- If **bacterial meningitis** still seems likely:
  - 16S rRNAPCR on CSF or blood
- If **viral meningitis** still seems likely:
  - Stool for enterovirus PCR
  - Throat swab for enterovirus PCR
  - CSF PCR for viruses directed by history eg Parechovirus
  - Consider other pathogens
  - PCR for MTb
  - Cryptococcalantigen test

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**Moving from first-line to secondary investigations**

- If any of the following features are present LP should be delayed:
  - Signs of severe sepsis or rapidly evolving rash
  - Respiratory or cardiac compromise
  - Anticoagulant therapy / known thrombocytopenia
  - Infection at the site of LP
  - Focal neurological signs
  - Presence of papilloedema
  - Continuous or uncontrolled seizures
  - GCS ≤12

  - Inability to see the fundus is not a contraindication to LP
  - LP may be safe at lower levels of consciousness

- Neuroimaging should be performed before LP for these indications

**Once the patient is stable and if meningitis is likely (with or without sepsis) an LP may still be diagnostically useful, even after several days.**

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**Fig 1. Investigations algorithm.** CSF = cerebrospinal fluid; CRP = C-reactive protein; Diff = white cell differential; GCS = Glasgow Coma Scale; Glu = glucose (CSF:blood ratio); HSV = herpes simplex virus; LP = lumbar puncture; MTb = Mycobacterium tuberculosis; PCR = polymerase chain reaction; Prot = CSF Protein; VZV = varicella zoster virus; rRNA = ribosomal ribonucleic acid
CME Infectious diseases

Step 1. Suspect pyogenic bacterial meningitis
(assuming Streptococcus pneumonia or Neisseria meningitidis)

a. Start ceftriaxone 2 g IV 12-hourly (or cefotaxime 2 g IV 6-hourly)
b. In patients with probable meningococcal sepsis not treated with ceftriaxone, give a single dose of ciprofloxacin 500 mg orally (to eliminate carriage)
c. In patients at risk for Listeria monocytogenes, such as patients with relative immunocompromise or old age, consider adding ampicillin/amoxicillin (step 2iiib).

If the patient has a history of anaphylaxis to cephalosporins or penicillin:
Step 1a. Start Chloramphenicol 25 mg/kg IV 6-hourly
Step 1c. Add in co-trimoxazole 10–20 mg/kg (of the trimethoprim component) in four divided doses.

Surveillance studies indicate invasive Listeria or Listeria meningitis is rare in immunocompetent adults aged under 60 years. Nevertheless, early meningitis guidelines recommend covering for Listeria in adults above 50 years of age.

Up-to-date information on countries exhibiting antibiotic resistance can be obtained via the European Centre for Disease Prevention and Control website or the World Health Organization (http://bit.ly/1Kosckx and http://bit.ly/1rOb3cx)

Step 2. Review after Gram stain

i. Gram-positive diplococci – likely Streptococcus pneumoniae
   a. Continue as step 1a (empiric treatment)
   b. If the patient visited a country with suspected penicillin resistance
      Add vancomycin 15–20 mg/kg IV 12-hourly until resistance data available
      Alternatively, add rifampicin 600 mg IV (or orally) 12-hourly
      Rifampicin should be used instead of vancomycin in renal failure

ii. Gram-negative diplococci – likely Neisseria meningitidis
   a. Continue as step 1a
   b. Add ampicillin/amoxicillin 2 g IV 4-hourly

iii. Gram-positive bacilli – suggestive of Listeria monocytogenes
   a. Continue as step 1a
   b. Add ampicillin/amoxicillin 2 g IV 4-hourly
   c. If high suspicion of extended spectrum beta lactamase (ESBL) resistance switch to meropenem 2 g IV 8-hourly

iv. Gram-negative rods – suggestive of Enterobacteriaceae
   a. Continue as step 1a
   b. Seek specialist advice on local antimicrobial resistance
   c. If high suspicion of ESBL resistance switch to meropenem 2 g IV 8-hourly

Step 3. Review when culture/PCR results available

i. Streptococcus pneumonia confirmed
   a. If penicillin sensitive (MIC ≤0.06 mg/L)
      Continue as step 1a (or switch to benzylpenicillin 2.4 g IV 4-hourly)
   b. If penicillin resistant (MIC >0.06) but cephalosporin sensitive
      Continue as step 1a
   c. If penicillin and cephalosporin resistant
      Add vancomycin 15–20 mg/kg IV 12-hourly and rifampicin 600 mg IV/orally 12-hourly
   d. If antibiotic sensitivity for organism not known (eg. pathogen PCR data only)
      Continue as step 2i (as for Gram-positive diplococci)
   e. In patients recovered by day 10, treatment should stop. Otherwise treat for 14 days
   f. In all cases of penicillin or cephalosporin resistance, treat for 14 days

ii. Neisseria meningitidis
   a. Continue as step 1a (or switch to benzylpenicillin 2.4 g IV 4-hourly)
   b. For patients recovered by day 5, treatment can stop

iii. Listeria monocytogenes
   a. Switch to ampicillin/amoxicillin 2 g IV 4-hourly
   b. Alternatively, give co-trimoxazole 10–20 mg/kg in four divided doses
      (of trimethoprim component) in patients with a history of anaphylaxis to beta lactams
   c. Treat for at least 21 days

iv. Haemophilus influenzae
   a. Continue step 1a
   b. Treat for 10 days

v. Enterobacteriaceae
   a. Continue as step 2i (for Gram-negative rods)
   b. Treat for 21 days

Fig 2. Three steps for antibiotic treatment in suspected pyogenic bacterial meningitis. IV = intravenous; MIC = minimal inhibitory concentration.
Few studies have examined outcome in viral meningitis. One recent study, reported one-third of adult varicella meningitis patients (3/9) suffered sequelae. In our experience, viral meningitis patients can suffer cognitive and psychological sequelae. Headaches occur in one-third of patients. Where there is concern, patients should access neuropsychological services, which can help detect subtle impairments and may facilitate functional recovery. Organisations such as the Meningitis Research Foundation (www.meningitis.org) or Meningitis Now (www.meningitisnow.org), can also provide helpful patient information and advocacy.

Conclusion

Many meningitis patients in the UK who have a CSF pleocytosis never have a pathogen identified. Clinicians need to remain vigilant and treat suspected bacterial meningitis promptly. However, with viruses being the most common cause of meningitis, rapid diagnosis via PCR can limit unnecessary antibiotic treatment and expedite hospital discharge.

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