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Have a high index of suspicion for meningitis in adults

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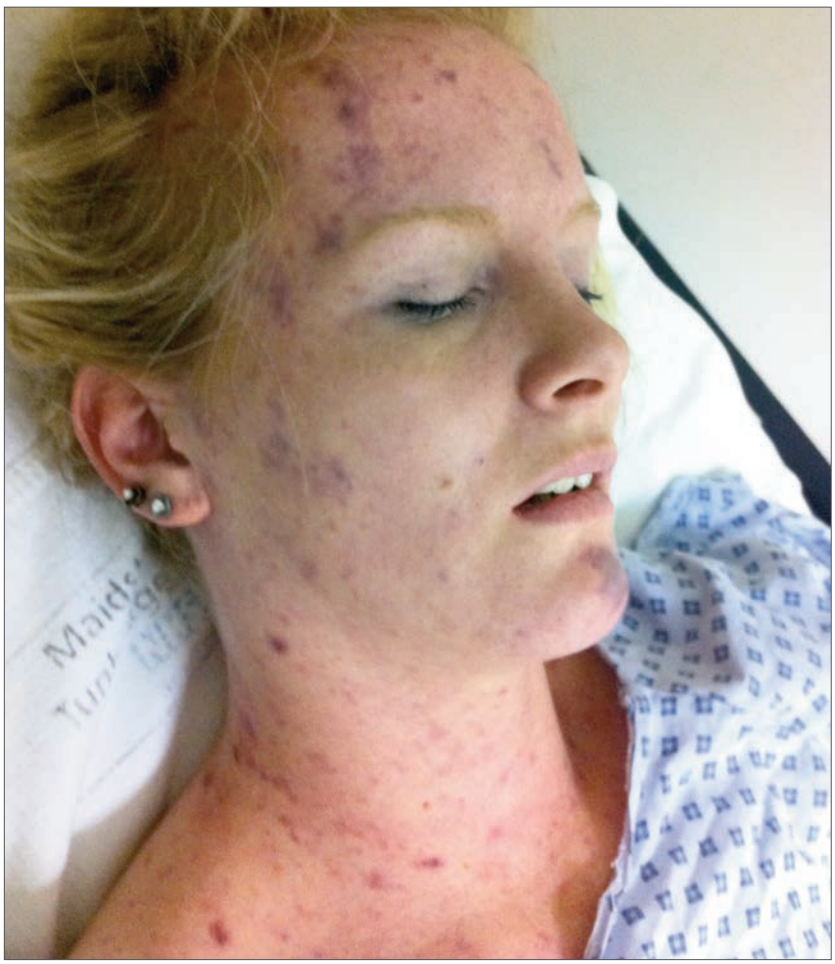

FIGURE 1
Meningococcal rash in a young woman

How do adults present with meningitis?

How should diagnosis be confirmed?

What are the treatment options?

BACTERIAL MENINGITIS AND MENINGOCOCCAL SEPSIS ARE RARE IN ADULTS. ANY DIAGNOSTIC delays with subsequent delay to treatment can have disastrous consequences.[1]

In recent years although there has been a reduction in the incidence of bacterial meningitis, this has been mainly in children. Over a similar timeframe there have also been changes in diagnostics. Hence the British Infection Association in partnership with other specialist societies formed a working group to revise their guidance on the management of meningitis in adults[2] and the new guidance was published in April 2016.[3]

These guidelines do not consider meningitis in immunocompromised individuals, post-surgical/iatrogenic meningitis or tuberculous meningitis. The management of bacterial meningitis in children and young people under the age of 16 is covered elsewhere.[4]

'The decline in bacterial meningitis over the past few decades has not been accompanied by a reduction in case fatality rate'

EPIDEMIOLOGY

The decline in bacterial meningitis over the past few decades has not been accompanied by a reduction in the case fatality rate[5,6] which can be as high as 20% for all causes of bacterial meningitis and 30% in pneumococcal meningitis.[7]

The number of cases of invasive meningococcal disease (including meningitis and meningococcal sepsis) has also been falling and is now half what it was some 20 years ago. The majority of cases are in young children with a second peak in adolescents and young adults.[8]

Since the inclusion of various conjugate vaccines in the routine UK vaccination schedule there have been significant reductions in meningitis caused by *Haemophilus influenzae* »

type b, *Streptococcus pneumoniae* and *Neisseria meningitidis* serogroup C. *S. pneumoniae* remains the predominant cause of community acquired meningitis in adults and *N. meningitidis* serogroup B is responsible for more than 80% of meningococcal disease.[8,9] England and Wales have been experiencing an epidemic of meningococcal disease caused by serogroup W.[10] Most cases occur in adults and there is often an atypical presentation including gastrointestinal symptoms.[11]

'The classic triad of neck stiffness, fever and altered consciousness is present in less than 50% of patients with bacterial meningitis'

The incidence of bacterial meningitis in adults in England and Wales has been estimated to be 1.05 per 100,000.[9] The incidence of viral meningitis has not been as clearly documented although is likely to be significantly higher. Viral meningitis is probably underdiagnosed and underreported.[12,13]

The most common causes in the UK are the enteroviruses and the herpes viruses (predominantly HSV-2 and VZV). Other less common viruses include cytomegalovirus, Epstein Barr virus and mumps virus. Herpes simplex virus type 1 more commonly causes encephalitis than meningitis.

While viral meningitis is rarely fatal in immunocompetent adults and is even frequently described as self-limiting, it can cause significant morbidity and also sequelae which may be underrecognised.[14-16]

Viral meningitis must not be confused with viral encephalitis – the former being infection of the meninges and the latter being infection of the brain parenchyma itself. The aetiology, pathogenesis, clinical features, treatment and most importantly prognosis are vastly different. There are recently published guidelines on the management of viral encephalitis.[17] Further definitions are given in table 1, right.

CLINICAL FEATURES

In a patient exhibiting the classic triad of neck stiffness, fever and altered consciousness, with headache and photophobia, vomiting and a petechial

Table 1

Definitions (adapted from the UK joint specialist societies guideline on the management of meningitis and meningococcal sepsis in immunocompetent adults)[3]

Meningism	Symptoms of headache, neck stiffness and photophobia often associated with meningitis
Meningitis	Inflammation of the meninges Strictly a pathological diagnosis Elevated CSF white cell count and protein are normally used as indicators of inflammation Meningeal enhancement may be seen on contrast-enhanced CT scan or MRI
Sepsis	Presence of infection with systemic manifestations such as: ● Fever or hypothermia ● Tachycardia ● Tachypnoea ● Altered mental state (see the Surviving Sepsis Campaign guidelines and also the recently published NICE clinical guideline on sepsis NG51 for a full list of potential manifestations of sepsis and recommendations on what to do in cases of suspected sepsis)[41,42]
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	Invasion of any normally sterile site by *Neisseria meningitidis* including meningitis and bacteraemia
Encephalitis	Inflammation of the brain parenchyma Strictly a pathological diagnosis Elevated CSF 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/negative bacterial PCR

CSF = cerebrospinal fluid; PCR = polymerase chain reaction; MRI = magnetic resonance imaging; CT = computed tomography

rash, diagnosis will be straightforward. However, many patients will not have these signs in combination. The classic triad is present in less than 50% of patients with bacterial meningitis.[7,18] These signs may frequently occur in isolation and in more minor, self-limiting illness so they can be poor discriminators for meningitis or meningococcal sepsis[19] posing a challenge for GPs.

Furthermore, clinical presentation may be different in specific populations. For example the elderly are more likely to have an altered level of consciousness but not exhibit other symptoms such as neck stiffness or fever.[20]

'A high index of suspicion for meningitis by the doctor or a family member is potentially an important indicator that the disease is present'

Patients with viral meningitis also present with signs of meningism (headache, neck stiffness, and photophobia) possibly with additional non-specific symptoms such as diarrhoea or sore throat. While they will not have a reduced level of consciousness (which would suggest an alternative diagnosis such as bacterial meningitis or viral encephalitis), it is clear there is an overlap with the symptoms of bacterial meningitis.

Invasive meningococcal disease can be considered on a spectrum. Meningococcal meningitis presenting with signs and symptoms of meningitis; meningococcal sepsis presenting with signs of sepsis including hypotension and classically a purpuric rash (see figure 1, p25), although the rash may take other forms, or be absent. Patients may of course have features of both. Mortality is higher in meningococcal sepsis but neurological and other long-term sequelae are more frequent in meningococcal meningitis.[21]

Examination should include neurological symptoms, particularly the level of consciousness, reduced Glasgow Coma Scale (GCS) score is a poor prognostic marker, signs of meningism and any focal neurology which may point to an alternative diagnosis. It is important to look for signs of shock and a careful examination of the skin is essential for evidence of a rash. Shock, coma and a rapidly progressive rash are all associated with a poor prognosis in meningococcal disease. Traditional signs such as Kernig's and Brudzinski's have poor sensitivity[22,23] and should not be relied upon to exclude, or make, a diagnosis of meningitis.

There is an overlap in symptoms and signs between viral and bacterial meningitis which often does not allow for reliable differentiation.[24] Hence all suspected cases of meningitis or meningococcal sepsis must be referred to hospital for further assessment and consideration of a lumbar puncture.[3]

ASSESSMENT

The challenge for GPs is to distinguish the minority of patients who have a life-threatening illness from those who have minor self-limiting infections. Careful assessment for clues as to the potential for invasive meningococcal disease or evidence of shock is paramount as this will help determine the urgency of hospital transfer as well as whether pre-hospital antibiotics are needed. There is also evidence, albeit in children, that a high index of suspicion for meningitis by the doctor or a family member is potentially an important indicator that the disease is present.[25]

Other factors that should specifically be enquired about are travel history, upper respiratory tract symptoms, especially otitis media, and contact with meningitis, sepsis or other infections.

PRE-HOSPITAL ANTIBIOTICS

The aim of pre-hospital antibiotics is to prevent any delay in antibiotic therapy which is known to be associated with increased mortality.[1,26] There are concerns about giving antibiotics in the community, including the risk of allergic reactions and decreased diagnostic yield following antibiotic administration. The majority of community patients with suspected meningitis will turn out to have viral meningitis or another viral illness with associated meningism and thus antibiotics should be reserved for those most likely to benefit from them.

Current evidence neither strongly supports nor refutes the use of pre-hospital antibiotics.[27,28] However, given the evidence that early antibiotics reduce mortality, antibiotics should be given in those cases where there is a strong suspicion of meningococcal disease (e.g. where a rash is present), signs of sepsis or of a poor prognosis such as an altered level of consciousness or seizures. If there is likely to be a delay in hospital admission of more than an hour antibiotics should be administered in the community.

Antibiotics should be given in the form of benzylpenicillin 1,200 mg im or iv or a third generation cephalosporin such as cefotaxime (2 g) or ceftriaxone (2 g) im or iv. It is obviously important to ensure that all antibiotics are in date.

In the case of known anaphylaxis to penicillins or cephalosporins, antibiotics should not be given until admission to hospital. Parenteral antibiotics should not delay transfer to hospital.[3]

REFERRAL

Urgent hospital referral is mandatory in all adults in whom meningitis or other forms of invasive meningococcal disease is suspected. This will allow a rapid assessment of whether a lumbar puncture is required and prompt administration of appropriate treatment. Transfer should be arranged via emergency ambulance such that patients arrive in hospital, ideally within an hour of assessment in the community. »

Table 2

Indications for neuroimaging before lumbar puncture (LP) in suspected meningitis (from the UK joint specialist societies guideline on the management of meningitis and meningococcal sepsis in immunocompetent adults)* [3]

- Focal neurological signs
- Presence of papilloedema **
- Continuous or uncontrolled seizures
- Glasgow Coma Scale score ≤ 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

CONFIRMING DIAGNOSIS

The value of early lumbar puncture cannot be stressed enough. This is key to establishing a definitive diagnosis, ensuring targeted treatment and minimising risks of overtreatment.

Ideally lumbar puncture should be performed before giving antibiotics (this is advocated if it can be performed within an hour of arrival at hospital) as yield rapidly reduces with potentially only 75% of lumbar punctures found to give a positive culture four hours post iv antibiotics and none positive at eight hours.[29]

Real world logistics however mean that many patients will have had treatment started prior to lumbar puncture. Therefore, if intravenous antibiotics have already been commenced, the lumbar puncture should still be performed as soon as possible, and preferably within four hours. Advances in the availability of bacterial CSF PCR may still establish the aetiology in culture-negative cases. However, this will not provide antibiotic sensitivity for the organism.

A significant factor in delayed lumbar puncture is the delay in neuroimaging, much of which may be unnecessary.[29] This has proved an area of practice resistant to change. Indications for neuroimaging prior to lumbar puncture are shown in table 2, p27. All other patients should have lumbar puncture as soon as possible.

'Early lumbar puncture is key to establishing a definitive diagnosis, ensuring targeted treatment and minimising risks of overtreatment'

The CSF cell count and Gram stain will be the first results available after lumbar puncture and can be key to diagnosis. Typically if the CSF leukocyte count is < 5 x 106 cells/L this excludes meningitis. Although approximately 1-2% of patients with bacterial meningitis may have a normal CSF white cell count. In addition to the initial cell count the CSF will also be cultured and analysed for total protein and glucose concentrations. PCR analysis for bacteria (*S. pneumoniae* and *N. meningitidis*) and viruses (HSV and VZV and enteroviruses) may also be performed.

Other investigations will include blood cultures, meningococcal and pneumococcal PCR on blood, serum glucose to pair with CSF glucose and a swab from the nasopharynx for evidence of *N.meningitidis*. This swab is useful for surveillance in case the CSF or blood cultures are rendered sterile by prior antibiotic use.

Typical CSF findings for viral and bacterial meningitis as well as encephalitis are compared in table 3, below.

MANAGEMENT

As discussed earlier, for patients seen in the community where there is a strong suspicion of meningococcal disease such as the presence of a rash or poor prognostic markers such as signs of sepsis, altered mental state or seizures, or where a delay in transfer to hospital is anticipated, antibiotics should be given prior to admission.

Antibiotic treatment

Empirical antibiotic choice is outlined in table 4, opposite. Certain groups will benefit from cover for Listeria (which is rarely seen in younger people) with additional ampicillin/amoxicillin.

Table 3

Classical CSF features of the different causes of meningitis (from the UK joint specialist societies guideline on the management of meningitis and meningococcal sepsis in immunocompetent adults) [3]

	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/μL)	< 5	Raised (typically >100)*	Raised (typically 5-1,000)*	Raised (typically 5-500)*	Raised (typically 5-500)*
Predominant cell type	n/a	Neutrophils**	Lymphocytes#	Lymphocytes†	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 those 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

* Occasionally the CSF WCC may be normal
** May be lymphocytic if antibiotics given before lumbar puncture (partially treated bacterial meningitis), or with certain bacteria e.g. *Listeria monocytogenes*
# May be neutrophilic in enteroviral meningitis (especially early in disease)
† May be neutrophils early on in the course of disease

These groups include: those over 60 years of age, patients with alcoholism, diabetes, malignancy or those who are on immunosuppressive therapy.[30]

Anti-listerial antibiotics are not routinely recommended for pre-hospital antibiotics as although *Listeria monocytogenes* is more common in these groups, *S. pneumoniae* is still by far the most frequent organism seen.

Return from travel (within the past six months) in an area of known penicillin-resistant pneumococcus will prompt the addition of vancomycin or rifampicin.

Chloramphenicol is recommended where there is a clear history of anaphylaxis to penicillins or cephalosporins.

In proven meningococcal meningitis or sepsis ceftriaxone, cefotaxime or high-dose benzylpenicillin is recommended. There is mounting evidence that shorter courses of treatment for meningitis, especially meningococcal, are not associated with a poor outcome.[31-33] If patients are slow to respond they may be given slightly longer courses.

Treatment should be discontinued after day 5 where patients have recovered. Similarly, treatment can be stopped for patients with a typical petechial/purpuric meningococcal rash but no identified organism who have recovered after day 5.

Finally in patients with pneumococcal disease who have recovered, treatment can be stopped after ten days. Normally, treatment is with ceftriaxone, cefotaxime or high-dose benzylpenicillin if the organism is susceptible.

Table 4

Empirical antibiotic choices (adapted from The UK joint specialist societies guideline on the management of meningitis and meningococcal sepsis in immunocompetent adults [3])

	Preferred choice	Alternative
Adults < 60 years of age	Cefotaxime 2 g 6 hourly OR Ceftriaxone 2 g 12 hourly	Chloramphenicol 25 mg/kg 6 hourly
Adults ≥ 60 years of age	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

Viral meningitis

While some physicians will treat herpes meningitis with aciclovir or valaciclovir, there is currently no evidence to support the use of antivirals in viral meningitis. Simple supportive measures and reassurance should be the mainstay of treatment.

Prophylaxis and secondary prevention

Meningitis is a notifiable disease and all cases must be reported. Secondary care will normally do this. The local health protection team will arrange prophylaxis for relevant contacts.[34] Treatment will differ according to aetiology.

Meningococcal infection

A single dose of ciprofloxacin is recommended for close contacts i.e. those living in the same household within the previous seven days and others such as 'mouth kissing contacts.'

- 500 mg for adults
- 250 mg for children aged 5-12 years
- 125 mg for children aged 1 month to 4 years

Rifampicin is only recommended for those unable to take ciprofloxacin at a dose of 600 mg twice daily for two days.

Of note, even after the use of prophylaxis, close contacts remain at additional risk for at least six months. It is therefore important that GP records of all close contacts are annotated to flag up this risk. Where contact has been with a case caused by a vaccine preventable serogroup, close contacts should be offered vaccination.[35]

Haemophilus influenzae type b

While *H. influenzae* meningitis is uncommon in adults, if infection is caused by a type b strain then in addition to close contacts receiving prophylaxis as above, vaccination should be given to all previously unvaccinated household contacts under ten years of age. Furthermore, in households where an at-risk individual resides, all household contacts should receive prophylactic rifampicin.

Pneumococcal infection

Close contacts of pneumococcal meningitis are not at increased risk and as such antibiotic prophylaxis is not required.

FOLLOW-UP

Most patients will fully recover. However, the sequelae of bacterial meningitis and meningococcal disease can be disabling. Problems are more likely to occur in pneumococcal meningitis than in meningococcal meningitis.[7,36] These problems may arise through direct neurological injury, or from tissue and organ damage secondary to sepsis. Headaches are frequently reported.[37] Both physical and psychological sequelae can have profound effects on the lives of patients' families as well as the patients themselves and it is therefore important to identify them so that appropriate treatment and support may be offered.

Notably careful assessment of hearing, cognition and mental health must be performed with any adverse findings addressed.[38,39] If this has not been carried out prior to discharge arrangements should be made by the GP. Specific NICE guidance exists to support management for all adults who have suffered a critical illness and may have spent time in critical care.[40]

'Sleep disorders, fatigue, headaches, and emotional problems are often reported in the weeks and months after discharge'

All patients with bacterial meningitis should be offered a hospital follow-up appointment within six weeks of discharge though GPs may pick up previously missed adverse sequelae requiring earlier assessment. Patients and families should be encouraged to seek support early if needed and should be provided with contact details of support and advocacy organisations, see Useful information box, p30.

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 straightaway. Fatigue, headaches, sleep disorders and emotional problems are often reported in the weeks and months after discharge.[15] Support from hospital clinicians and »

SPECIAL REPORT
MENINGITIS IN ADULTS

key points

SELECTED BY

Dr Matthew Lockyer
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Bacterial meningitis and meningococcal sepsis are rare in adults. Any diagnostic delays with subsequent delay to treatment can have disastrous consequences. The decline in bacterial meningitis over the past few decades has not been accompanied by a reduction in case fatality rate which can be as high as 20% for all causes of bacterial meningitis and 30% in pneumococcal meningitis.

***S. pneumoniae* remains the predominant cause of** community acquired meningitis in adults and *N. meningitidis* serogroup B is responsible for > 80% of meningococcal disease. England and Wales have been experiencing an epidemic of meningococcal disease caused by serogroup W. Most cases occur in adults and there is often an atypical presentation including GI symptoms. The classic triad of neck stiffness, fever and altered consciousness is present in < 50% of cases of bacterial meningitis. These signs may frequently occur in isolation and in more minor, self-limiting illness.

Patients with viral meningitis also present with signs of meningism (headache, neck stiffness and photophobia) possibly with additional non-specific symptoms such as diarrhoea or sore throat. While they will not have a reduced level of consciousness (which would suggest an alternative diagnosis such as bacterial meningitis or viral encephalitis), it is clear there is an overlap with the symptoms of bacterial meningitis. Mortality is higher in meningococcal sepsis but neurological and other long-term sequelae are more frequent in meningococcal meningitis.

Suspected cases of meningitis or meningococcal sepsis must be referred for further assessment and consideration of a lumbar puncture. The challenge for GPs is to distinguish the minority of patients who have a life-threatening illness from those who have minor self-limiting infections. Early lumbar puncture is key to establishing a definitive diagnosis, ensuring targeted treatment and minimising risks of overtreatment. Ideally lumbar puncture should be performed before giving antibiotics.

There is currently no evidence to support the use of antivirals in viral meningitis. Simple supportive measures and reassurance should be the mainstay of treatment. Meningitis is a notifiable disease and all cases must be reported. Secondary care will normally do this. The local health protection team will arrange prophylaxis for contacts. Treatment will differ according to aetiology.

Most patients will fully recover. However, the sequelae of bacterial meningitis and meningococcal disease can be disabling. Problems are more likely to occur in pneumococcal meningitis than in meningococcal meningitis. Many patients feel well at discharge and do not realise that they may not be able to return to all their normal duties and activities straightaway. Fatigue, headaches, sleep disorders and emotional problems are often reported in the weeks and months after discharge. GPs can help with this and enable patients to stage their return to work or studies on a part-time basis at first.

Disclaimer
FM is an NIHR doctoral research fellow. 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.

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Useful information

Meningitis Research Foundation
www.meningitis.org

Meningitis Now
www.meningitisnow.org

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