Management of meningitis

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Meningitis occurs mostly in previously fit young people and, because it causes significant mortality and morbidity, must be recognised and treated promptly. Overall, the mortality of bacterial meningitis in adults is 25%, with significant sequelae of disease including deafness and cognitive loss.[1] In bacterial meningitis, the first step in pathogenesis is colonisation of the nasopharynx, followed by haematogenous spread to other sites including the meninges.[2] In viral meningitis, acquisition is mostly faecal-oral, followed by viraemia.

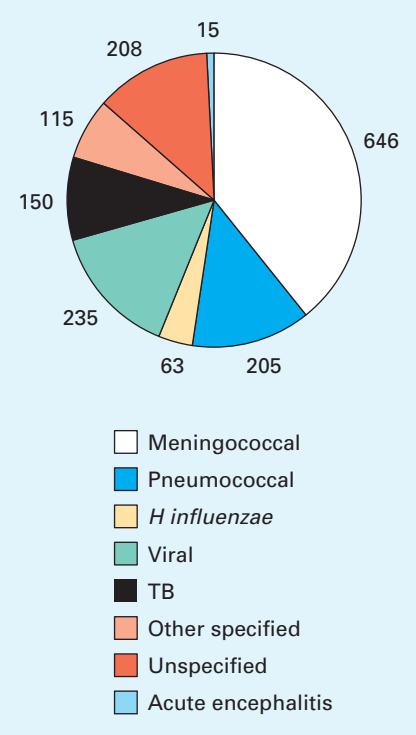

Fig 1. Notifications of all causes of meningitis to the Health Protection Agency in 2003.[3]

Incidence

The prevalence of meningitis cases notified to public health from 1991–2003 in England and Wales, stratified by microbiological aetiology, is shown in Fig 1. Most reported cases are bacterial (Fig 2), the most common pathogens now being *Neisseria meningitidis* and *Streptococcus pneumoniae*,[3] although aetiology varies with age. Cases due to Gram-negative organisms such as *Escherichia coli* and *Klebsiella* spp[1] have increased over the last four decades, reflecting nosocomial infections through advancing neurosurgical and oncological procedures.

The impact of vaccines

Significant recent advances have been the introduction of vaccines against *Haemophilus influenzae* type B (Hib) and *N. meningitidis* serogroup C. Routine immunisation with these vaccines began in the UK in 1992 and 1999, respectively, with impressive reductions of disease (Fig 3). There is currently no vaccine for *N. meningitidis* serogroup B, now responsible for most meningococcal disease in the UK. In the USA, the incidence of invasive pneumococcal disease has fallen significantly since the deployment of the 7-valent conjugate pneumococcal vaccine introduced in 2001.

Each modern conjugate vaccine targets capsular polysaccharides and reduces nasopharyngeal colonisation by bacteria expressing the cognate capsular antigen. The concern that this might lead to 'serotype replacement', in which disease caused by bacteria with hitherto uncommon capsule types emerges, has not been substantiated.

The availability of vaccine varies widely worldwide and bacterial meningitis is still a major cause of mortality and morbidity in poorer countries. For example, in the World Health Organization African region *H. influenzae* causes an estimated 100,000–160,000 child deaths each year. *S. pneumoniae* causes 250,000–400,000 child deaths per year and *N. meningitidis* is responsible for large epidemics (causing thousands of deaths) in many West and Central African countries.[4]

Clinical features

Symptoms of bacterial meningitis can develop over a matter of hours. Patients

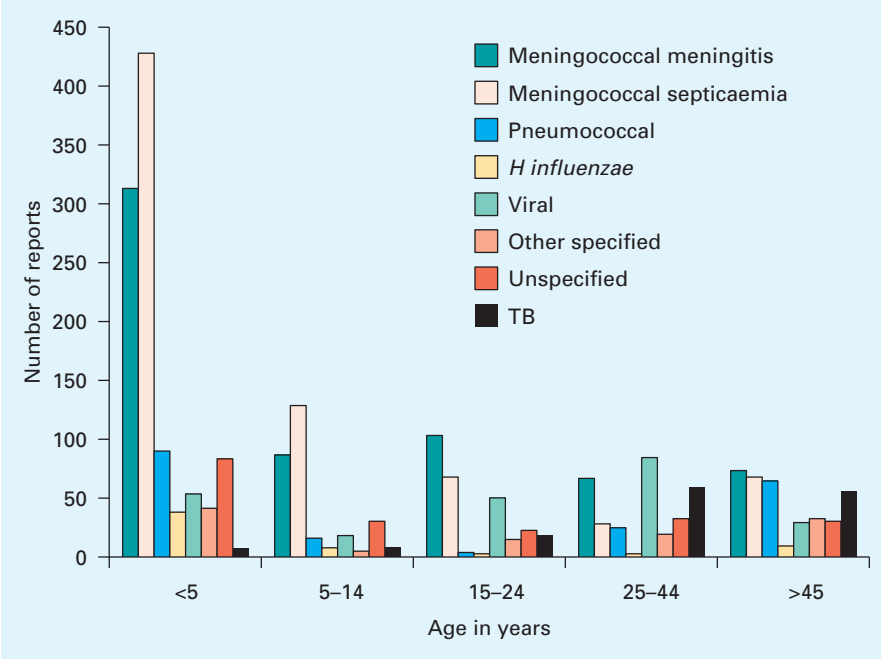

Fig 2. Aetiology of meningitis by age group in England and Wales, 2003.[3]

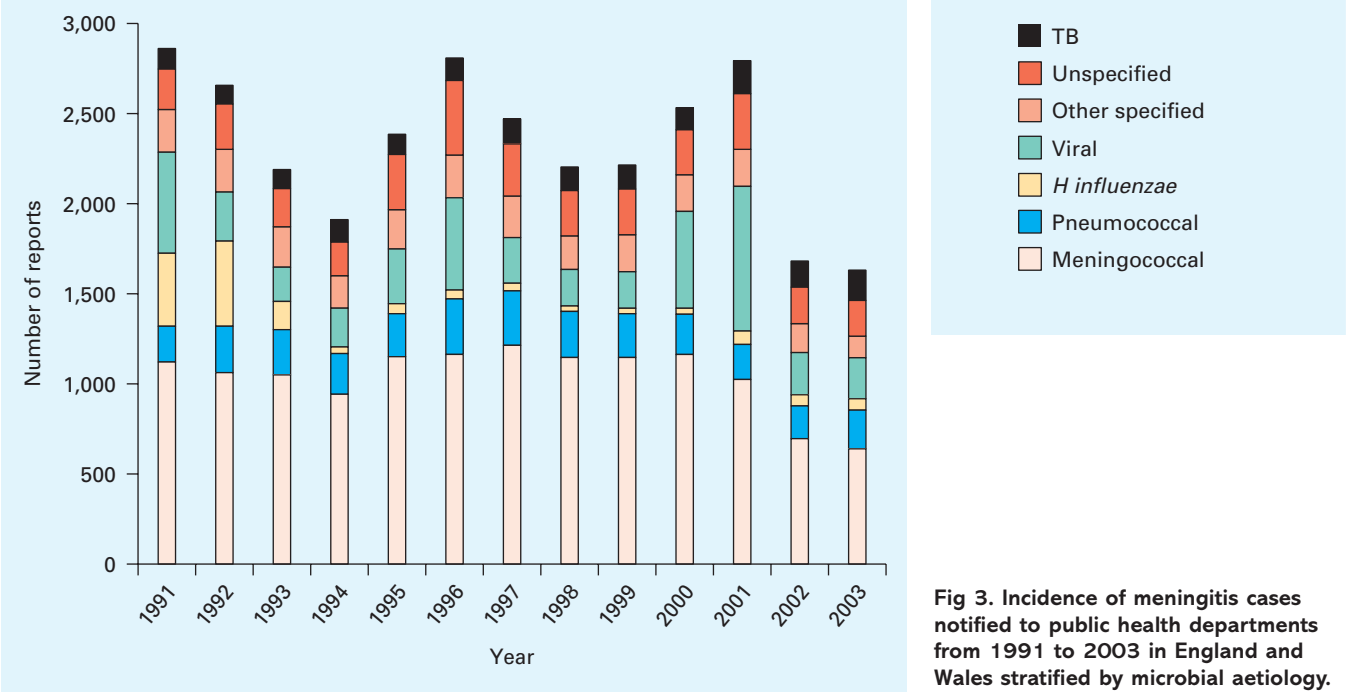

Fig 3. Incidence of meningitis cases notified to public health departments from 1991 to 2003 in England and Wales stratified by microbial aetiology.

may complain of extreme malaise and myalgia before signs of meningism or septicaemia develop. The classic signs of headache, nuchal rigidity, fever and/or focal neurological signs are often absent in the immunocompromised and patients at the extremes of age. Meningitis should be considered in any ill baby or elderly person without an obvious diagnosis. The underlying microbiological aetiology may be suspected from the clinical history (Tables 1 and 2).

Diagnosis

All patients with suspected meningitis should undergo lumbar puncture (LP) to obtain cerebrospinal fluid (CSF) for laboratory analysis. Classic CSF results are summarised in Table 3. Contraindications to LP include raised intracerebral pressure (Fig 4), local topical infection and bleeding diatheses. Cranial computed tomography (CT) prior to LP is not necessary routinely unless there are:

- clinical signs of raised intracranial pressure:[5]
- focal neurological signs
- falling Glasgow coma score
- history of head trauma.

Routine laboratory tests should include full haematological and biochemical screening and blood cultures (Table 4). CSF and whole blood samples should be sent for polymerase chain reaction (PCR), a test with 88.4%, 100% and 91.8% sensitivity for the diagnosis of *N. meningitidis*, *H. influenzae* and *S. pneumoniae*, respectively.[6]

Management of bacterial meningitis

The administration of parenteral antibiotics (usually benzylpenicillin) in the community is standard practice for suspected meningitis in the UK.[7] In penicillin allergy, the risk/benefit of an anaphylaxis history (absolute contraindication), the degree of diagnostic suspicion and rapidity of access to secondary care should be considered. Cefotaxime or chloramphenicol are acceptable alternatives (Table 5).[8]

In hospital, delivery of empiric parenteral antibiotics should not be delayed for clinical investigation such as CT of the head or lumbar puncture, as delay can significantly increase mortality and morbidity.[9,10] Cefotaxime is the empiric antibiotic of choice for most patients (Tables 6 and 7).[11,12] Modification case-by-case could include adding vancomycin if there is concern about penicillin-resistant pneumococci or *Staphylococcus aureus*, or high-dose ampicillin if listeriosis is suspected, particularly in neonates, the elderly and the immunosuppressed.[13]

Use of steroids

The routine use of steroids in the management of bacterial meningitis in children[14] has declined over the last decade following Hib vaccine introduction, with some evidence from the tropics of adverse effects.[15] Considerable controversy also exists over the benefit of steroids in adults. A recent multicentre randomised controlled trial revealed moderate benefit for patients with all causes of bacterial meningitis, but subgroup analysis of patients with pneumococcal disease revealed a significant reduction in adverse outcome.[16] Therefore, current advice is that steroid use is justified if there is a strong suspicion of pneumococcal disease.[11]

Chemoprophylaxis for contacts

Local public health departments should be notified of all cases of meningitis; they will coordinate administration of prophylaxis to household contacts of

Table 1. Pathogens associated with meningitis.

Causes	Pathogen		Common risk factors
Bacterial	*Neisseria meningitidis*: serotypes	A	Epidemic meningitis in central Africa
		B	Students and young adults
		C	As above, not vaccinated with MenC
		W157	Pilgrims to the Hajj, Saudi Arabia
	Streptococcus pneumoniae		Head injury, sinusitis, CSF leak, elderly, alcoholism
	Haemophilus influenzae B		Children especially <1 year, not vaccinated with HiB, very elderly, head injury, CSF leak
	Listeria monocytogenes		Neonates, elderly, diabetes, consumption of unpasteurised milk and meat products, immunosuppression, especially with steroids
	Group B Streptococcus		Neonates and infants <3 months
	Klebsiella spp		Premature and low birthweight neonates
	Escherichia coli		
	Klebsiella spp		Post-traumatic/neurosurgical/nosocomial
	Escherichia coli		
	Staphylococcus aureus		
	Coagulase-negative staphylococci		
	Pseudomonas aeruginosa		
	Acinetobacter spp		
	Streptococcus suis		Hong Kong/Thailand, occupational exposure to pigs
Viral	*Herpes simplex* virus		Cutaneous HSV lesions, past or present
	Varicella zoster virus		Shingles or chicken pox
	Enterovirus spp		Diarrhoea, contact with small children
	Mumps virus		Parotitis, not vaccinated with MMR
	Poliomyelitis		Indian subcontinent, not vaccinated with OPV
	HIV		Primary infection or advanced immunodeficiency
Mycobacterial	TB		Previous exposure to TB, associated with HIV
Fungal	*Cryptococcus neoformans*		Immunosuppression, especially with HIV
Protozoal	*Naeglerii fowleri*		Swimming in affected fresh water lakes, mainly Australia
Treponemal	*Treponema pallidum*		Secondary, tertiary, quaternary syphilis

CSF = cerebrospinal fluid; HiB = *Haemophilus influenzae* type B; HSV = herpes simplex virus; MenC = meningitis C; MMR = measles, mumps, rubella triple vaccine; OPV = oral polio vaccine; TB = tuberculosis.

Table 2. Clinical picture of meningitis.

Cause	Clinical picture	Rapidity of onset
Bacterial:		
neonates/younger children	Miserable, poor feeding, vomiting, 'floppy baby', bulging fontanelle, convulsions	1–24 hours
adults/older children	Headache, fever, neck stiffness, photophobia, shock, seizures, focal neurology Petechial rash in meningococcal septicaemia	1–24 hours
Viral meningitis	Headache, malaise, neck stiffness, mild photophobia Usually contact with small children	>24 hours
Viral encephalitis	Headache, malaise, confusion, nominal aphasia	12–24 hours
Tuberculous	Insidious onset headache, weight loss, night sweats, occasionally cough, focal neurology often late onset	>4 weeks
Fungal	Headache, malaise, mild fever, occasionally confusion	2–3 weeks
Protozoal	Meningo-encephalitis: fever, vomiting, headache, neck stiffness, coma Rapid progression to death within 1 week	1–2 days
Treponemal	Usually asymptomatic in secondary syphilis, descending tract signs in tabes dorsalis	Months to years

Table 3. Cerebrospinal fluid analysis.

Cause	Predominant leukocytes	WCC/µmol	Glucose (cf serum glucose)	Protein
Normal	Lymphocytes	<5	ca 2/3	<400 g/dl
Bacterial	Polymorphonucleocytes*	50–5,000	99	88
Viral	Lymphocytes	10–200	6	8
Tuberculous	Lymphocytes	50–500+	9	88
Fungal	Lymphocytes	10–200	9/6	8
Protozoal	Polymorphonucleocytes	400–26,000	9/6	8
Treponemal	Lymphocytes	10–200	9	8

* Lymphocytic picture predominates in meningitis due to *Listeria monocytogenes*.
WCC = white cell count.

Table 4. Laboratory tests to be requested at presentation.

Laboratory test	Sample required	Test request
Full blood count	Whole blood (EDTA)	FBC
Full biochemical profile	Serum (plain or gel tube)	U&Es, LFTs
Coagulation screen	Plasma (citrate)	Clotting screen
Inflammatory markers	Serum (plain or gel tube)	CRP
Blood cultures	Culture medium	Blood cultures
Meningococcal antigen	Whole blood, CSF, throat swab	Meningococcal PCR
Acute phase serology	Serum (plain or gel tube)	?meningitis, save serum
Enterovirus	Faeces, throat swab	Enterovirus culture
Pneumococcal antigen	Urine, CSF, blood, throat swab	Pneumococcal antigen

CRP = C-reactive protein; CSF = cerebrospinal fluid; EDTA = ethylenediamine tetraacetic acid; FBC = full blood count; LFT = liver function test; PCR = polymerase chain reaction; U&E = urea and electrolytes.

patients affected by *N. meningitidis* or *H. influenzae*. Chemoprophylaxis reduces nasal carriage of these pathogens, which can be as high as 50% in contacts of meningococcal disease.[17] For contacts of meningococcal infection over 12 years old, a single dose of ciprofloxacin is appropriate. Children below the age of 12 and contacts of *H. influenzae* should receive rifampicin 10 mg/kg 12 hourly for two days (5 mg/kg for those under 1 year).[8]

Management of tuberculous meningitis

Symptom onset in tuberculous meningitis is often insidious, with headache, lethargy, fever, weight loss and night sweats. Many patients will have evidence of tuberculosis (TB) elsewhere, often with an abnormal chest radiograph. Laboratory confirmation can be difficult as the yield of *Mycobacterium tuberculosis* from CSF is low. If clinical suspicion is high, treatment should be initiated without waiting for further laboratory results as untreated tuberculous meningitis carries a 100% mortality. Samples of CSF should be sent for prolonged culture for TB, as should sputum (obtained by induction with hypertonic saline if necessary) and early morning urine samples.

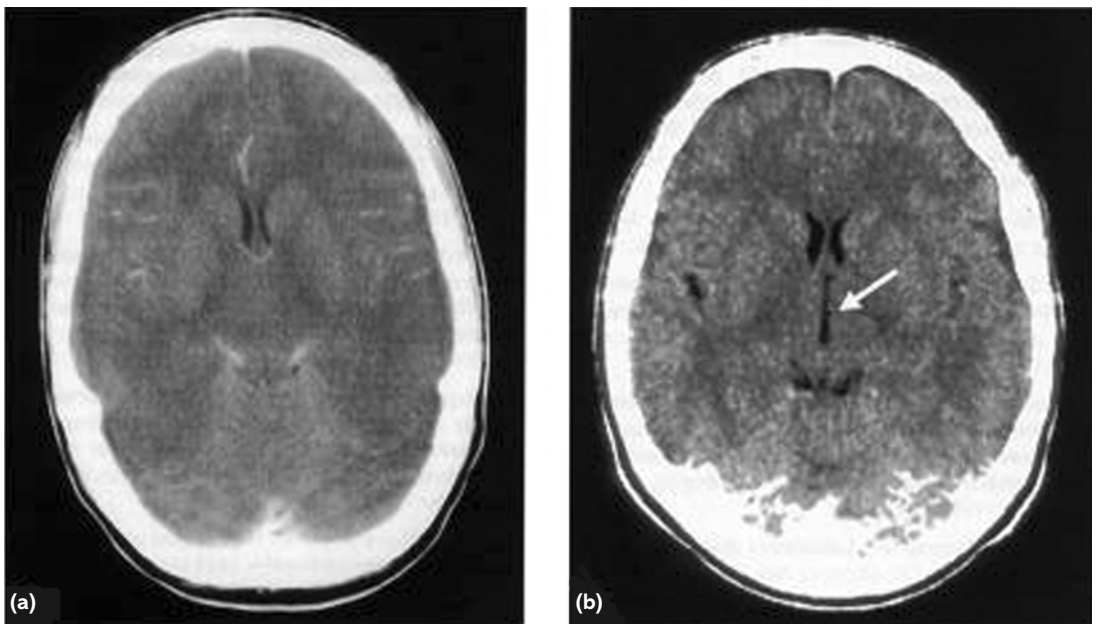

Fig 4. Cerebral oedema in bacterial meningitis. Computed tomography scan of brain of a young patient with meningitis **(a)**. There is severe cerebral oedema: the third ventricle is obliterated when compared with the third ventricle (arrow) of a normal individual **(b)**.

Unless there is a high suspicion of multidrug resistant TB (MDRTB), 12 months of standard TB therapy is appropriate,[18] with doses calculated by weight (Table 8). Paradoxically, tuberculous lesions can expand in early treatment and tuberculous meningitis is associated with cerebral microabscesses, therefore steroids should be prescribed at the initiation of therapy. As with all TB, there is an increased incidence of coinfection with HIV and patients should be counselled and tested accordingly. Expert advice should be sought for management of MDRTB.

Table 5. Parenteral therapy prior to hospitalisation.

Therapy	Age	Dose
Benzylpenicillin	Child <1 year Child 1–10 years Adult and child >10 years	300 mg 600 mg 1.2 g
Cefotaxime	Child <12 years Adult and child >12 years	50 mg/kg 1 g
Chloramphenicol	Child <2 weeks Adults and child >2 weeks	25 mg/kg 50 mg/kg

Management of viral meningitis

Viral meningitis, also known as aseptic meningitis, is usually a self-limiting illness. Enteroviridae such as Coxsackie B and echovirus are the most common cause in immunocompetent patients. Clinical meningism and headache, which can be striking, are often temporarily alleviated by LP. Pleconaril, an antiviral agent with activity against enteroviridae, is currently under evaluation. Other causes of viral meningitis, such as mumps, varicella zoster, herpes simplex (HSV) and cytomegalovirus follow a similar clinical pattern. Mollaret's meningitis is a rare syndrome of recurrent aseptic meningitis due to HSV. It is self-limiting, although frequent episodes may warrant the use of prophylactic acyclovir.

Herpes simplex meningo-encephalitis is a different entity to HSV meningitis, carrying an untreated mortality of 60–80%. Classic presenting symptoms include headache, fever, confusion, word finding difficulties and epileptiform seizures. Patients may present at any age, often without a history of clinical

Table 6. Empiric treatment of bacterial meningitis in children.

	Suspected pathogens	Antibiotic treatment	Dose	Frequency	Duration	Adjunctive therapy
Neonates and infants <3 months	Group B *streptococcus* *Listeria monocytogenes* *Escherichia coli*	Cefotaxime Ampicillin	150 mg/kg 50 mg/kg	Divided doses 6 hourly	2 weeks	Consider addition of gentamicin in <1 month old
Children and infants >3 months	*Neisseria meningitidis* *Streptococcus pneumoniae* *Haemophilus influenzae B*	Cefotaxime *or* Ceftriaxone	200 mg/kg/day 100 mg/kg/day	Divided doses Once daily	2 weeks	Consider use of dexamethasone 0.15 mg/kg 12 hourly for 2 days; start with or just before 1st dose of antibiotics

Table 7. Empiric treatment of suspected bacterial meningitis in adults.

Suspected bacteria	Intravenous antibiotic therapy	Dose	Frequency	Duration	Adjunctive therapy
Meningococcus	Cefotaxime *or* Ceftriaxone	2 g 2 g	6 hourly daily	5 days	Consider use of activated protein C if severe sepsis
Pneumococcus	Cefotaxime *or* Ceftriaxone *plus* Vancomycin (if high level of penicillin resistance)	2 g 2 g 1 g	6 hourly daily 12 hourly	14 days	Dexamethasone 0.15 mg/kg iv qds for 4 days; start with or just before 1st dose of antibiotics
Other Streptococcus spp	Cefotaxime *or* Ceftriaxone	2 g 2 g	6 hourly daily	14 days	Consider possibility of intracranial abscess
Haemophilus influenzae	Cefotaxime *or* Ceftriaxone	2 g 2 g	6 hourly daily	14 days	Consider ENT review if sinusitis or otitis media
Listeria	Ampicillin	2 g	4 hourly	14 days	Reduce immunosuppression if appropriate
Nosocomial infection	Meropenem *plus* Vancomycin	1 g	12 hourly	14 days	Consider need for neurosurgical intervention if cerebral shunt related

Note: If there is any doubt about the causative organism, cover all possible pathogens.
ENT = ear, nose and throat.

Table 8. Tuberculous meningitis therapy for all patients.

	Dose				
	Adults	Children	Frequency	Duration	Adjunctive therapy
Isoniazid	<50 kg 450 mg >50 kg 450 mg	5–10 mg/kg (max 300 mg)	Daily	12 months	Prednisolone 60 mg daily for 2 weeks, then tail off slowly
Rifampicin	<50 kg 450 mg >50 kg 600 mg	10 mg/kg (max 600 mg)	Daily	12 months	
Pyrazinamide	<50 kg 1.5 g >50 kg 2 g	35 mg/kg	Daily	2 months	
Ethambutol	15 mg/kg	15 mg/kg	Daily	2 months	

herpes labialis. Antiviral therapy should be instituted early with intravenous acyclovir, 10 mg/kg eight hourly. CSF analysis may be unhelpful but PCR for HSV on CSF is highly sensitive and specific.[19] Additional diagnostic tools include electro-encephalography (EEG), classically showing slow spike and wave activity, and magnetic resonance imaging of the brain, which may reveal early temporal lobe changes. Parenteral therapy should continue for two weeks as CSF penetration of oral acyclovir is insufficient.

Meningitis in the immunocompromised host

Bacteria are the most common cause of meningitis in immunocompromised patients, particularly pneumococcal disease in Africa, and *Listeria monocytogenes* in the immunosuppressed. Meningitis due to *Cryptococcus neoformans* has increased in incidence since the onset of the AIDS pandemic, but was well recognised previously in both immunocompetent people and those compromised by lymphoreticular malignancies and transplants (both solid organ and bone marrow). Treatment is with flucytosine and amphotericin B. Expert specialist opinion should be sought at the earliest opportunity.

Human immunodeficiency virus (HIV) alone can cause viral meningitis, most commonly as part of a seroconversion illness. Advancing HIV disease leads to increased risk of many infections, including meningitis due to TB, cytomegalovirus and toxoplasma as well as *C. neoformans*. Timely involvement of physicians trained in HIV medicine is vital.

Future trends

Further development and deployment of effective vaccines, including novel meningococcal and pneumococcal vaccines, will be required to reduce the burden of bacterial meningitis. The most urgent need is for a vaccine against serogroup B meningococcus. Immunomodulators have been shown to be capable of influencing outcomes in meningitis, but more precise tools will be required in the future.

Key Points

- **Bacterial meningitis continues to have a 25% mortality in adults**
- **Vaccines against meningitis C and *Haemophilus influenzae* type B have significantly reduced disease from these pathogens**
- **New evidence suggests benefit in the use of steroids in pneumococcal meningitis**
- **Laboratory techniques such as polymerase chain reaction have increased accurate detection of pathogens**

KEY WORDS: antibiotics, bacterial, meningitis, vaccines, viral

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The returned traveller

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UK residents made almost 60 million visits abroad in 2002, three times the number in 1981. Most were to the European Union but there were over four million visitors to tropical or near-tropical areas, and since 1995 there has been a steady increase in UK travel to Asia, the Caribbean and South and Central America. The number of travellers to sub-Saharan Africa has risen only slightly. However, there has been a marked increase in immigration from Africa and the distinction between traveller and immigrant is irrelevant to the acute medical team.

The public usually expects to be immunised against infections such as typhoid and hepatitis A before travelling to more exotic destinations but are largely unaware that avoiding the more significant threats to health and life depends more on their behaviour abroad and on prompt presentation to informed doctors should they become ill on return.

What is special about returned travellers?

Returned travellers most commonly present with fever, skin lesions, diarrhoea, jaundice or anxiety that they may be incubating an infection. Febrile patients require the most urgent assessment.

Being confronted with a patient recently returned from overseas can be a daunting experience for doctors concerned that they may miss unfamiliar but urgent life-threatening conditions. Although returned travellers present with a variety of symptoms, the possibility of a fatal outcome is virtually confined to those with fever. A safe management protocol for such patients is identical to what should be followed in managing any acutely febrile patient, with the important addition, when appropriate, of urgent investigation for falciparum malaria coupled with preparedness to treat for malaria even when a negative result is obtained. Timing is of the essence: treated early, malaria is simple to cure but delays of only a few days can allow progression to severe disease with full-blown sepsis necessitating intensive care.

The standard protocol for febrile patients (see below) includes a chest X-ray; this usually shows non-lobar consolidation in patients with legionellosis, often when pneumonia would not have been thought likely from the patient's symptoms. Approximately half of notified Legionnaires' disease in the UK occurs in returned travellers and the infection kills as many such individuals each year as falciparum malaria.

Key Points

- **The most urgently life-threatening conditions in returned travellers are falciparum malaria, leptospirosis and Legionnaires' disease**
- **Early treatment of life-threatening infection is vital and circumstantial evidence often justifies treatment before the diagnosis can be confirmed**
- **Reference to incubation periods is helpful in diagnosing conditions that are rarely or never acquired in the UK**
- **Primary HIV infection is increasingly recognised as a cause of fever in returned travellers. HIV testing should readily be offered**

KEY WORDS: foreign travel, Legionnaires' disease, malaria, primary HIV infection