

Community-acquired acute meningitis and encephalitis: a narrative review

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Infection of the central nervous system, usually presenting as meningitis or encephalitis, is a medical emergency that rapidly progresses to death in as many as 40% of patients; survivors may have long term deficits of neurological function.^{1,2} Comprehensive reviews of this topic have recently been published,^{1,3} as have management guidelines.⁴⁻⁶ In this article, I focus on developments in the field since my previous review,⁷ particularly on developments of local relevance. Meningitis and encephalitis may co-exist (as meningo-encephalitis) or share symptoms (headache and fever) and aetiologies, but I will discuss the two entities separately. Understanding the rationale of management protocols requires a foundation in the epidemiology and microbiology of encephalitis and meningitis, topics that will be concisely reviewed.

PubMed, Google Scholar and the Cochrane Library were searched for original research and review articles published during 2002–2018. Specialist society publications and guidelines⁴⁻⁶ were also consulted in order to formulate an evidence-based overview relevant to clinical practice.

Meningitis

Epidemiology

A total of 1.3 million cases of meningitis worldwide are reported around the world each year.⁸ The incidence in Geelong (Victoria) during 2011–2013 was 8.9 cases per 100 000 person-years; seven of the 52 patients had bacterial meningitis, 16 viral meningitis.⁹

Streptococcus pneumoniae (pneumococcus) is the main cause of bacterial meningitis in children and adults worldwide; of 1636 invasive pneumococcal infections in Australia during 2016, meningitis was diagnosed in 126 cases.¹⁰ Pneumococci with reduced susceptibility to penicillin are isolated in 10–12% of cases of invasive disease in Australia, which is important when discussing empiric treatment protocols.¹¹

The epidemiology of *Neisseria meningitidis* (meningococcus) differs between geographic locations: serogroup A predominates in the sub-Saharan “meningitis belt” (specific vaccination against this pathogen is recommended for travellers to Africa and the Middle East), serogroup B in most developed countries. In 2015, 53 of 182 patients with invasive meningococcal infections in Australia had meningococcal meningitis.¹² The proportion of serogroup W invasive meningococcal infection cases in Australia has recently risen to 42.5%; serogroup B accounts for 36.1%, serogroup Y for 15.9%, and serogroup C for 1.2% of cases.¹³

Streptococcus agalactiae (group B streptococcus) is a major cause of neonatal meningitis, usually acquired from the mother during vaginal delivery.⁵

Listeria monocytogenes has historically been the third most frequent cause of neonatal meningitis (after group B streptococci

Summary

- Meningitis and encephalitis are medical emergencies. Patients need prompt evaluation and immediate empiric therapy to reduce the likelihood of fatal outcomes and chronic neurological sequelae.
- Conjugate bacterial vaccines have significantly reduced the incidence of bacterial meningitis, especially in children.
- As the results of changes in patterns of bacterial drug sensitivity, ceftriaxone is now part of the recommended empiric treatment for bacterial meningitis and should be administered as early as possible.
- Neuroimaging delays the treatment of meningitis and is not needed in most cases.
- Adjunctive corticosteroid therapy is of benefit for many patients with meningitis and should be initiated in most adults before antibiotic therapy.
- Molecular testing can assist the specific diagnosis of encephalitis and should be based on the exposure history and geographic risk factors relevant to the patient, but non-infectious causes of encephalitis are also common.
- Empiric therapy for encephalitis should be directed at the most frequently identified infectious pathogen, herpes simplex virus type 1 (ie, intravenous aciclovir).
- Vaccines can protect against the major pathogens of childhood infections (measles, mumps, rubella, polio, varicella viruses), influenza viruses, and exotic pathogens that cause meningitis and encephalitis (rabies, Japanese encephalitis, dengue, yellow fever, tick-borne encephalitis viruses, *Mycobacterium tuberculosis*).

and *Escherichia coli*),⁵ but its prevalence in Europe has recently fallen.¹⁴ It is an important cause of meningitis in older and immunocompromised people, including organ transplant recipients and people with diabetes, cancer, alcohol misuse, or human immunodeficiency virus (HIV) infection.

Viral meningitis is usually caused by enteroviruses or herpes simplex virus type 2 (HSV-2).¹⁵

Clinical features

Fever, nuchal rigidity, and altered mental state comprise the classic clinical triad of meningitis, but are present in fewer than half of patients.¹ A petechial rash, seen in a large proportion of cases,¹⁶ suggests meningococcal infection,¹ but other meningeal pathogens (eg, *S. pneumoniae*) can cause similar rashes.⁵

Assessing children with possible meningitis is often difficult, as signs and symptoms are often non-specific (poor feeding, irritability, hyper- or hypotonia).⁵ A low threshold for referral to specialist care is therefore appropriate; children who present with frank septicaemia need immediate treatment and referral.

Clinical investigations

Cerebrospinal fluid (CSF). Abnormal CSF findings are made in 88% of cases of bacterial meningitis (Box 1), but 6% of neonates,

1 Typical cerebrospinal fluid (CSF) findings in cases of suspected meningitis and encephalitis

	Reference range	Bacterial meningitis ^{1,5}	Viral meningitis ¹⁷	Encephalitis ¹⁷
Gram staining		Positive: 25–90% of cases (highest rates: <i>S. pneumoniae</i> , <i>N. meningitidis</i> ; lowest rates: <i>L. monocytogenes</i>)	Negative	Negative
White cell count	0–5 × 10 ⁶ /L	> 2000 × 10 ⁶ /L (neutrophil predominance)	5–1000 × 10 ⁶ /L (lymphocytic predominance)	5–1000 × 10 ⁶ /L (lymphocytic predominance)
Protein	0.15–0.45 g/L	> 2.2 g/L	0.5–1 g/L	0.5–1 g/L
Glucose	<ul style="list-style-type: none"> 2.5–4.4 mmol/L CSF/serum ratio > 0.6 	<ul style="list-style-type: none"> < 1.9 mmol/L, or CSF/serum ratio < 0.23 	Normal	> 2.7 mmol/L
Polymerase chain reaction		<ul style="list-style-type: none"> Useful if undertaken before antibiotic therapy Positive: 61–100% of cases (<i>S. pneumoniae</i>, 61–100%, <i>N. meningitidis</i>, 88–94%) 	Preferred investigation	Preferred investigation
Bacterial culture		Positive: 50–96% of cases (lower if antibiotic therapy received)	Negative	Bacterial or fungal encephalitis: positive; Other aetiologies: negative

25% of patients with *Listeria* infections, and 2% of adults with meningitis have normal CSF values.^{1,5-7} Twenty-five per cent of patients with cancer complicated by meningitis have white cell counts below 100 × 10⁶/L.¹

The sensitivity of routinely employed rapid antigen tests is insufficient to alter decisions about empiric management of untreated and pre-treated patients.⁵ It has been suggested that CSF lactate levels distinguish between bacterial and viral meningitis, but they can also be elevated in patients with encephalitis.⁵

Blood cultures. Blood cultures should be undertaken, and are positive for the causative organism in 40–100% of patients with meningitis who are unable to have lumbar puncture because of anticoagulation treatment, elevated intracranial pressure, signs of brain shift, space-occupying lesions, or other reasons, and are essential for diagnosis and decision-making.^{1,18}

Brain imaging. Brain imaging prior to lumbar puncture is now common practice, but is only required for patients who have focal neurological signs, seizures, or altered mental state or who are immunocompromised.¹ Most patients should undergo lumbar puncture without a potentially fatal delay.¹

Treatment of bacterial meningitis

Empiric therapy. Antibiotics should be given within an hour of the patient arriving in hospital; delayed administration is an important cause of death among patients with bacterial meningitis.¹ The choice of initial antibiotic therapy is influenced by the local community prevalence of pathogens, especially of pneumococci with reduced penicillin susceptibility. Penicillin is no longer a generally appropriate empiric therapy for meningitis.⁵ Treatment protocols should be conservative because of the severe consequences of an inappropriate antibiotic choice, particularly as the causative pathogen is initially unknown (Box 2). Pneumococci with reduced penicillin susceptibility are also resistant to other antibiotics; in some countries (eg, South Africa) the rate of ceftriaxone resistance is so high that meropenem is instead employed in empiric meningitis therapy,⁵ a situation that could also develop in Australia.

The current Australian Therapeutic Guidelines (version 15) recommendations for empiric treatment of suspected bacterial meningitis⁴ are summarised in Box 3. The guideline recommendations, however, can be difficult to implement, and introducing a meningitis care bundle in hospitals may better streamline management.¹⁹

2 Essential management principles for patients with suspected acute meningitis or encephalitis

- Severe headache, fever and altered mental state should arouse suspicion of acute meningitis or encephalitis
- Meningism, photophobia and petechial rash favour the diagnosis of meningitis
- Early onset of altered cognition, especially with temporal lobe features, suggests encephalitis
- Infants with meningitis may have non-specific features (poor feeding, irritability, hyper- or hypotonia) and should be referred for assessment as soon as possible
- Blood cultures should be attempted in all suspected cases of suspected meningitis or encephalitis
- Lumbar puncture should be performed unless there are contraindications (eg, bleeding diathesis)
- Computerised tomography (CT) is initially required only for patients with suspected elevated intracranial pressure (papilloedema, focal signs, seizure, deteriorating consciousness state) or who are immunocompromised; CT scanning should not delay initiation of antibiotic therapy
- Polymerase chain reaction (PCR) testing is required if blood cultures are negative or the patient has already received antibiotic therapy
- Diagnostic uncertainty warrants initially following the meningitis management pathway ♦

3 Empiric treatment guidelines for patients with suspected bacterial meningitis, Australia⁴

- Empiric antibiotic treatment should not be withheld if it is anticipated that investigations will cause a delay greater than 30 minutes
- For empiric therapy of bacterial meningitis: ceftriaxone (adults, 4 g/day; children, 50 mg/kg, to maximum 2 g/day)
- If gram-positive cocci are identified in cerebrospinal fluid (CSF) by gram staining, or otitis media or sinusitis are suspected, intravenous vancomycin should be added until the penicillin minimum inhibitory concentration (MIC) is known
- Amoxicillin should be added to the empiric protocol for patients at increased risk of *Listeria* meningitis (neonates, older, pregnant or immunocompromised patients, people with comorbid conditions) until CSF culture results are known
- Adjunctive dexamethasone (10 mg) should be given to adult patients before or together with the first antibiotic dose
- Chemoprophylaxis of household contacts of patients with meningococcal infections: ciprofloxacin (adults, 500 mg peroral immediately; children, 30 mg/kg) or rifampicin (adults, 600 mg peroral twice daily for 2 days; children, 5–10 mg/kg); ceftriaxone (250 mg intramuscular) is preferred for pregnant women. ♦

Specific therapy. This should be based on the drug sensitivity of the identified causative organisms, as determined by microbiological analysis.

Adjunctive therapies. These are often added to specific therapies to avert particular complications:

- *Antibiotics:* See [Box 3](#).
- *Rifampicin:* An uncontrolled multicentre study in France found that adding rifampicin to standard empiric meningitis protocols was beneficial.²⁰
- *Corticosteroids:* Adjunctive corticosteroid therapy was reported to be beneficial for children with meningitis during the period when the predominant paediatric pathogen was *Haemophilus influenzae* serogroup B;²¹ after vaccination eliminated *H. influenzae* as a significant pathogen, this benefit was no longer evident.²² The findings of three Cochrane reviews of the value of adjunctive corticosteroid therapy for meningitis (2003–2010)^{22–24} changed with shifts in pathogen prevalence and patient characteristics, but most individual studies found clear benefits (reduced mortality). The 2010 Cochrane review²² found that the rates of severe hearing loss, any hearing loss, and short term neurological sequelae in patients with acute bacterial meningitis were significantly reduced in high income countries (Europe, North America, Australia) by adjunctive corticosteroid therapy; the mortality associated with pneumococcal meningitis was also significantly reduced, and no significant adverse effects of corticosteroid therapy were noted. The authors recommended that bacterial meningitis in high income countries be treated with corticosteroids, before or together with the first antibiotic dose. Corticosteroid therapy has, however, been associated with increased mortality in patients with *Listeria* meningitis.²⁵
- *Induced hypothermia and glycerol therapy* were associated with lower survival in randomised studies of bacterial meningitis, and are therefore not recommended.²⁰
- *Intracranial pressure-targeted treatment* improved outcomes for patients with bacterial meningitis in one study,¹ but its role in routine practice is yet to be defined.¹
- *Anticonvulsants:* In the absence of seizures, there is no role for prophylactic anticonvulsant therapy for patients with meningitis.⁵

Treatment of viral meningitis

Viral meningitis (most commonly caused by an enterovirus) is generally milder than bacterial meningitis and has a benign course unless complicated by encephalitis or myelitis. Recurring episodes of aseptic (ie, non-bacterial) meningitis should prompt investigation for HSV-2 — with a prevalence of up to 12% in the general

population in Australia,²⁶ its contribution to meningitis in this country is not well explored — and treatment with intravenous aciclovir. Viral suppression with valaciclovir does not prevent relapsing HSV-2 meningitis.²⁷ Other causes of aseptic meningitis include medications (antibiotics, non-steroidal anti-inflammatory agents, chemotherapies), autoimmune disorders (especially systemic lupus erythematosus), neurosurgery, and seizures.²⁸

Most patients with viral meningitis can be managed at home with analgesics, but they should be advised to return to hospital promptly if their condition deteriorates significantly. Pleconaril has been available for treating enteroviral meningitis since 2006,²⁹ but did not gain Food and Drug Administration approval in the United States because of its modest effect and poor cost–benefit relationship.^{29,30} Treatment of chronic meningo-encephalitis in immunocompromised patients with pleconaril was reported to be promising,³⁰ but some viral strains are drug-resistant.³¹ These limitations, and the usually benign course of viral meningitis, have prevented widespread adoption of the drug.

Prevention

Conjugate vaccines (10- and 13-valent vaccines are available in Australia) have reduced the prevalence of the pneumococcus among children in most countries¹ and, to a lesser degree, adults (relative risk of hospitalisation for pneumococcal meningitis [2010 v 1997], United States: children under 12 months of age, 0.166; adults aged 18–44 years, 0.380).³²

The group C meningococcal conjugate vaccine has been funded by the Australian government since 2009; serogroup C meningococci were responsible for 5.8% of meningococcal cases in 2008.³³ The group B conjugate vaccine targets a more prevalent bacterial serotype, but requests for federal subsidisation have been repeatedly declined because of its cost and the low prevalence of meningococcal disease in Australia (the vaccine is, however, government-funded in the United Kingdom). In light of recent outbreaks, Victoria, Western Australia, and the Northern Territory have subsidised vaccines that also protect against the W-serotype (A/C/W/Y quadrivalent vaccine).¹³

After conjugate vaccines against *S. pneumoniae*, *N. meningitidis* and *H. influenzae* group B were introduced, the number of deaths attributed to these organisms worldwide have fallen by 29%, 25%, and 45% respectively.¹ *H. influenzae* group B vaccination programs drive serogroup replacement, as indicated by the increased numbers of cases of non-group B *H. influenzae* meningitis.⁵

Antenatal screening during the third trimester to identify women colonised by group B streptococci and intrapartum treatment with intravenous penicillin reduced the incidence of neonatal

meningitis and sepsis in early studies, but more recent investigations have found this strategy to be ineffective.⁵

Encephalitis

Encephalitis has been characterised as an acute infective encephalopathy with at least three of the following features: fever (> 38°C), seizures, focal neurological signs, CSF pleiocytosis (white blood cell count > 5 × 10⁶/L), electro-encephalogram (EEG) slowing, and abnormal magnetic resonance imaging (MRI) findings.^{17,34}

Epidemiology

The global incidence of encephalitis is estimated to be 1.7–7.4 cases per 100 000 person-years.³⁵ In New South Wales, the annual hospitalisation rate for encephalitis during 1990–2007 was 5.2 cases per 100 000 population, with a mortality rate of 4.6%.³⁶ A specific aetiology was documented in only 30.4% of cases; herpes simplex virus (12.9% of hospitalisations), varicella zoster (3.8%), and *Toxoplasma gondii* (3.7%) were the causal pathogens most frequently identified.³⁶ A retrospective study in England reported that herpes simplex virus (HSV), varicella zoster virus, and adenoviruses were the most frequently identified infective causes.³⁷ A subsequent prospective study in England highlighted the significant contribution (21%) of acute disseminated encephalomyelitis and auto-antibody mediated encephalitis to the total case load.³⁵

A recent large retrospective multicentre study of adults in whom HSV was detected in the CSF by polymerase chain reaction (PCR) confirmed that HSV-1 generally causes encephalitis and HSV-2 meningitis, although each subtype can cause both syndromes.³⁸

Immunosuppressed patients are at particular risk of infection by human herpes virus (HHV)-6 (particularly HHV-6B),³⁹ HHV-8, Epstein–Barr virus, cytomegalovirus, varicella zoster virus,⁴⁰ JC virus, BK virus, lymphocytic choriomeningitis virus, *T. gondii*,⁴¹ *Bartonella*, and *Cryptococcus*. Reactivation of JC virus underlies progressive multifocal leukoencephalopathy, a syndrome which was initially recognised as a complication of HIV infection, but is increasingly seen as a consequence of medical immunosuppression (including with natalizumab and rituximab).⁴²

The spinal cord and peripheral nerve roots can also be infected by recognised encephalitis pathogens, including viruses (poliovirus, enteroviruses, varicella zoster virus, cytomegalovirus, human T-cell leukaemia virus [HTLV-1], influenza viruses), bacteria (*Mycobacteria*, *Borrelia*, *Treponema* spp.), fungi (*Cryptococcus*, *Coccidioides* spp.) and parasites (*Toxoplasma*, *Trypanosoma*, *Schistosoma*, *Echinococcus* spp.). As they are not all notifiable pathogens, their community prevalence must often be inferred from surrogate data, such as those collected by the Australian Paediatric Surveillance Unit (eg, the annual rate of non-polio acute flaccid paralysis during 1995–2015 was 1.04 cases per 100 000 population).⁴³

Encephalitis not directly caused by an acute infection should be considered in the differential diagnosis, including immunological conditions such as acute demyelinating encephalomyelitis and the growing spectrum of auto-antibody-mediated and paraneoplastic conditions.⁴⁴

Clinical features

Headache, fever, and altered mentation are the clinical hallmarks of encephalitis, but meningism (in meningo-encephalitis), seizures, cranial nerve and brainstem signs, movement disorders, temporal

lobe features (micro- or macropsia, olfactory hallucination, behavioural change) may co-exist and provide insights into the aetiology (online Appendix, table 1).³

A comprehensive history should include the speed of progression of the illness, vaccination status of the patient, unusual exposures (ill relatives, animal exposures [including bites], freshwater exposure), arthropod bites, travel history, and eating and sexual habits.⁷

Clinical investigations

Blood cultures and CSF analysis should be undertaken before initiating therapy.⁷ CSF cell count and protein and glucose content should be measured, and the presence of bacteria (including mycobacteria) and fungal pathogens assessed by culturing and PCR, according to patient history and exposures and the local prevalence of pathogens. Although certain CSF findings are typical for encephalitis (Box 1), a confirmed laboratory diagnosis is frequently not obtained.⁶ Specific CSF serology tests can be helpful if syphilis, flavivirus, or *Cryptococcus* infections are likely; blood serology tests for HIV, syphilis, and flaviviruses should be requested if indicated by exposure history. Respiratory and stool specimens for PCR assessment may be also be informative (enteroviruses, influenza A and B viruses, adenoviruses, parvoviruses, rotaviruses).

Chest X-ray (if tuberculosis, cryptococcosis or melioidosis are likely), electroencephalography (to exclude epilepsy and other encephalopathy), and central nervous system (CNS) imaging (preferably MRI, especially in immunosuppressed patients) are usually required; significant inter-observer variation in the interpretation of neuroimaging scans, however, has been reported.⁴⁵ Some parasites cause space-occupying lesions (*Toxoplasma*, *Taenia solium*, *Schistosoma*, *Gnathostoma*) rather than regional or diffuse inflammation.⁴⁶

Treatment

Supportive therapy. Intensive care is usually required for close observation of the patient and the control of intracranial pressure and seizures, circulatory and respiratory support, and maintenance of fluid and electrolyte balance.

Empiric therapy. Until the results of specific investigations are available, the patient should receive intravenous aciclovir (adults, 10 mg/kg, 8-hourly; infants under 3 months of age, 20 mg/kg, 8-hourly; infants, 3 months to 12 years, 500 mg/m²); if encephalitis is confirmed, aciclovir therapy should be continued for 14–21 days. If meningeal signs are present, antibiotics (ceftriaxone [4 g/day] with amoxicillin [8 g/day] intravenous) should be initiated until the results of bacterial cultures are known.⁷

Specific therapy. *Toxoplasma* encephalitis is the most frequent cause of CNS lesions in people with acquired immunodeficiency syndrome (AIDS), usually after reactivation of a latent infection.³⁸ The standard therapy (sulfadiazine and pyrimethamine) is associated with significant toxicity; a recent meta-analysis did not find this regimen to be superior to alternatives such as clindamycin and pyrimethamine or sulfamethoxazole and trimethoprim.⁴⁷ Treatment choices for individual patients with AIDS may therefore deviate from the usually recommended sulfadiazine–pyrimethamine combination because of allergy or toxicity.⁴⁸

Ganciclovir has some efficacy in infants with congenital cytomegalovirus infections with neurological complications, but it is not yet clear which patients benefit most.⁴⁹

Future adjunctive therapies. Animal models of herpes encephalitis have suggested that adjunctive corticosteroid therapy could be beneficial; a clinical trial in Germany examined whether it augmented the effect of acyclovir.⁵⁰ Artesunate and rapamycin proved useful as adjuncts to valaciclovir therapy in a mouse model of herpes encephalitis,⁵¹ and clinical studies should be considered.

Prevention

Australian travellers to overseas countries may be exposed to exotic encephalitis pathogens, many of which can be prevented by vaccination (online Appendix, table 2). Japanese encephalitis⁵² and rabies virus vaccines⁵³ are especially recommended for travellers who plan to spend more than one month in areas where these diseases are endemic. The first inactivated Japanese encephalitis virus vaccine (JE-Vax) had potentially serious side effects, but more recent inactivated (JEspect) and live/attenuated (Imojev) vaccines appear to be better tolerated.⁵³ Many childhood diseases historically regarded as causes of encephalitis (measles, mumps, polio, varicella) are now prevented by routine vaccinations.⁵⁴

Varicella zoster virus can cause serious CNS vascular lesions and encephalitis, particularly in older and immunocompromised people.⁴⁰ A double strength live varicella zoster virus vaccine (Zostavax) boosts immunity in previously exposed people with 69% efficacy, declining to 4% after 8 years;⁵⁵ in immunocompromised recipients it can elicit CNS effects similar to those of natural infection.⁵⁶ An inactivated varicella zoster virus vaccine (Shingrix) has greater efficacy than Zostavax⁵⁵ — number of individuals needed to be vaccinated to prevent one case: killed vaccine, 6–14; live vaccine, 21–138⁵⁷ — but it is not yet licensed in Australia.

An animal vaccine against the Hendra virus (Equivac) may reduce risks to humans by reducing animal infections, and is recommended by the Australian Veterinary Association.⁵⁸

Because of the close taxonomic relationship between Australian bat lyssavirus and rabies virus, rabies vaccine is included in Australian protocols for protecting humans from acquiring bat lyssavirus from pteropid (fruit bat) vectors.⁵⁹

Conclusions

- Vaccines that prevent infection by pathogens which cause meningitis and encephalitis should be employed comprehensively.
- A low threshold of suspicion for diagnosing bacterial meningitis is required, and empiric treatment should be initiated without delay.
- The indications for adjunctive corticosteroid treatment of patients with bacterial meningitis are unclear, but many patients benefit from this approach. The first dose should be administered very early in management.
- Encephalitis can be elicited by a range of infectious and non-infectious causes. Managing patients with encephalitis is complex, and specialist advice should be sought as early as possible. Empiric therapy with aciclovir for the most frequently identified treatable cause of encephalitis (HSV-1) should be initiated without delay.

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