



# Aseptic meningitis: a foundation review

*Hazim Allos and Rodrigo Hasbun*

## Purpose of review

This review addresses the multifaceted nature of aseptic meningitis, a condition with diverse infectious and noninfectious etiologies. Despite its common presentation in clinical settings, over half of the cases remain without an identified cause, necessitating a comprehensive examination of diagnostic and management strategies. The increasing availability of advanced molecular diagnostics and the challenge of distinguishing bacterial from nonbacterial cases make this an opportune time to explore its implications for clinical practice.

## Recent findings

The literature highlights the pivotal role of advanced molecular diagnostics, such as multiplex PCR and metagenomic sequencing, in improving the identification of pathogens in aseptic meningitis. Enteroviruses remain the leading cause, but pathogens like Herpesviridae, arboviruses, and nonviral agents such as fungi and spirochetes also contribute significantly. New diagnostic algorithms and clinical models are emerging to distinguish bacterial from viral meningitis, reducing unnecessary treatments.

## Summary

Aseptic meningitis management is evolving with advancements in diagnostic technologies that allow for earlier pathogen identification, improving patient outcomes and minimizing healthcare costs. These findings underscore the importance of timely and accurate diagnostics and tailored therapeutic strategies in both clinical and research settings. Enhanced awareness of noninfectious causes is also crucial for comprehensive care.

## Keywords

advanced molecular diagnostics, aseptic meningitis, cerebrospinal fluid analysis, infectious and noninfectious etiologies, viral and bacterial differentiation

## INTRODUCTION

The term “aseptic meningitis syndrome,” introduced by Swedish physician Wallgren in 1925, describes meningitis cases without an identifiable bacterial cause [1]. It involves acute, community-acquired meningitis with cerebrospinal fluid (CSF) pleocytosis, a negative Gram stain, and no parameningeal focus or systemic illness. Inflammation involving the brain, with focal neurological signs, is called encephalitis, while involvement of the meninges and brain is termed meningoencephalitis [2<sup>•</sup>].

Over half of aseptic meningitis cases lack an identified cause [2<sup>•</sup>]. When identified, viruses – particularly enteroviruses – are the most common pathogens. Although often used interchangeably, “aseptic meningitis” is broader than “viral meningitis,” encompassing cases caused by nonviral infectious agents and noninfectious factors [2<sup>•</sup>]. This review summarizes its etiology, pathophysiology, clinical presentation, diagnosis, management, and prognosis.

## INITIAL EVALUATION

A detailed history is crucial in identifying causes of aseptic meningitis, focusing on recent mosquito or tick bites, high-risk sexual behaviors, endemic travel, medication use, immunosuppression, and exposure to illness.

Symptom patterns differ by age: adults typically report headaches (99%), nausea/vomiting (75%), neck stiffness (50%), photophobia (46%), malaise (35%), and respiratory symptoms (11%), while children more often present with fever (87%), nausea/vomiting (63%), headache (60%), respiratory symptoms (31%), photophobia (27%), neck stiffness (24%), and malaise (7%) [3].

Department of Medicine, Section of Infectious Disease, McGovern Medical School, UT Health Science Center, Houston, Texas, USA

Correspondence to Hazim Allos, 6410 Fannin St., Houston, TX 77030, USA. Tel: +1 617 283 0866; e-mail: Hazim.Allos@uth.tmc.edu

**Curr Opin Infect Dis** 2025, 38:261–270

DOI:10.1097/QCO.0000000000001105

## KEY POINTS

- Definition and scope: Aseptic meningitis is defined as meningitis with cerebrospinal fluid pleocytosis, negative Gram stain, and no identifiable bacterial cause, including viral, nonviral infections, and noninfectious etiologies.
- Clinical presentation: Aseptic meningitis generally presents with milder symptoms than bacterial meningitis, with key features like gradual onset headache, nausea, and neck stiffness; altered mental status may suggest other conditions like encephalitis; however, CSF analysis needs to be obtained to better evaluate the cause.
- Diagnostic advances: Advanced molecular diagnostics like multiplex PCR significantly improve pathogen detection, even in cases where traditional methods fail, while metagenomic next-generation sequencing shows promise but requires further study to establish its routine clinical viability.
- Diagnostic considerations: While advanced tests like multiplex PCR offer high sensitivity and specificity for many pathogens, clinicians should interpret results within the clinical context, as false negatives and positives can occur depending on the test and the pretest probability of disease.
- Therapeutic approaches: Empiric antimicrobial treatment, including adjunctive dexamethasone in bacterial cases, is critical, while supportive care remains the mainstay for viral causes; rapid diagnostics and scoring systems aid in minimizing unnecessary antibiotic use.

Most cases have normal Glasgow Coma Scale scores and neurologic exams. Unlike bacterial meningitis, which presents acutely within 24 h, aseptic meningitis usually has a gradual onset and milder symptoms. Altered mental status, focal deficits, or seizures may indicate bacterial meningitis, brain abscess, or encephalitis [4]. A lumbar puncture for CSF analysis is recommended to confirm the diagnosis.

Certain physical examination findings help assess meningeal irritation in suspected meningitis:

- (1) Kernig Sign: Flex the hip to 90° and extend the knee; pain or resistance past 135° in the lower back or thigh.
- (2) Brudzinski Sign: Reflexive knee and hip flexion upon neck flexion.
- (3) Jolt Accentuation of Headache: Headache worsens with rapid side-to-side head rotation.

Brudzinski's neck sign, initially reported with 97% sensitivity, and Kernig's sign, with 57%

sensitivity in the preantibiotic era, now demonstrate significantly lower sensitivities, sometimes as low as 5%, though both retain high specificity [5,6]. In contrast, jolt accentuation remains with 65.3% sensitivity and 70.4% specificity [7].

## DIAGNOSIS AND CHALLENGES

The initial evaluation of suspected meningitis requires prompt lumbar puncture to measure opening pressure, perform cell count and differential, and assess glucose, protein, Gram stain, and bacterial culture. Further molecular and advanced testing is guided by clinical suspicion.

Gram stain and culture remain the gold standard for diagnosing bacterial meningitis, as molecular techniques do not cover all pathogens, and culture is crucial for antibiotic susceptibility testing. Gram stain sensitivity ranges from 50 to 90% with 100% specificity, but sensitivity drops to 10–15% if the culture is negative [8–10]. CSF sterilization from prior antimicrobial therapy can occur rapidly, sometimes within an hour, though other CSF abnormalities persist longer [11].

The typical CSF profile in aseptic meningitis includes protein levels of 50–300 mg/dl, white blood cell (WBC) counts of 5–1000 cells/μl with lymphocytic predominance, normal to low-normal glucose levels, and normal opening pressure. Early viral meningitis may exhibit neutrophilic predominance in up to 25% of cases, transitioning to lymphocytic predominance as the disease progresses [12,13]. Certain bacterial infections, like *Listeria monocytogenes* and *Mycobacterium tuberculosis*, and some fungal pathogens can also present with lymphocytic predominance [14,15].

Advanced molecular diagnostics, like multiplex PCR, are increasingly valuable in meningitis evaluation. The BioFire FilmArray detects 14 pathogens, including *E. coli* K1, *H. influenzae*, *L. monocytogenes*, *N. meningitidis*, *S. pneumoniae*, *S. agalactiae*, cytomegalovirus, enterovirus, HSV-1/2, human herpesvirus 6, human parechovirus, varicella-zoster virus, and *Cryptococcus neoformans/C. gattii*, using only 0.2 ml of CSF. Results are available in 1 h, with 90% sensitivity and 97% specificity [16,17]. False negatives are common for HSV-1/2 and cryptococcal meningitis, while false positives are often linked to *S. pneumoniae* and occasionally *H. influenzae* [18,19]. For low clinical suspicion, a negative multiplex PCR result may exclude meningitis. However, for high suspicion of specific pathogens, singleplex PCR offers greater accuracy, such as enterovirus PCR (96% sensitivity, 99% specificity) [20], human parechovirus PCR (100% sensitivity and specificity) [21], and HSV-1/2 PCR (98.9% sensitivity, 97.1% specificity) [22].

Metagenomic next-generation sequencing (mNGS) analyzes all genetic material in a sample, detecting pathogens without prior targeting. In a study of 204 patients, including 57 with CNS infections, mNGS diagnosed 22% of cases missed by standard methods and confirmed 19 of 45 diagnoses alongside standard diagnostics [23]. Though not yet standard care, mNGS can be valuable depending on the suspected etiology. Nucleic acid-based diagnostics detect pathogens even when staining and culture are negative, especially after antimicrobial therapy. Unlike cultures, they identify nucleic acids from nonviable organisms [16,24]. However, the duration of nucleic acid detectability after organism death or treatment remains unclear, warranting further research.

The initial evaluation of suspected meningitis includes a complete blood count, typically normal in viral meningitis but showing significant leukocytosis in bacterial cases. Blood cultures are crucial, with positivity rates up to 90% in bacterial meningitis, depending on the pathogen and prior antibiotic use [3,10]. Elevated serum procalcitonin levels further support a bacterial meningitis diagnosis, as levels are usually normal in nonbacterial cases [25,26].

## DIAGNOSTIC CRITERIA

Aseptic meningitis, as defined by the International Brighton Collaboration Aseptic Meningitis Working Group, is diagnosed based on clinical signs such as fever, headache, vomiting, or nuchal rigidity, combined with CSF pleocytosis ( $>5$  WBC/ $\mu$ l in patients  $\geq 2$  months or  $>15$  WBC/ $\mu$ l in those  $<2$  months). Diagnosis is stratified into three levels of certainty. Level 1 requires a negative Gram stain and culture without prior antibiotic use. Level 2 allows for negative cultures despite prior antibiotics or when no culture is performed. Level 3 applies when diagnostic criteria overlap with encephalitis and is classified as encephalitis if parenchymal inflammation dominates the clinical or diagnostic findings [27]. In cases of traumatic lumbar puncture, pleocytosis is confirmed if the observed WBC count exceeds the predicted value, calculated as (CSF RBC count)  $\times$  (Blood WBC / Blood RBC), to account for contamination [27].

## IMAGING

Head imaging in suspected meningitis cases is usually unremarkable or shows subtle findings, such as meningeal enhancement, which rarely alter the clinical approach. The Infectious Diseases Society of America (IDSA) recommends a head CT scan

before lumbar puncture in adults with risk factors such as immunosuppression, a history of CNS conditions (e.g., mass lesion, stroke), recent-onset seizures, papilledema, altered mental status, or focal neurological deficits.

In patients without these risk factors, blood cultures and a lumbar puncture should be performed promptly, followed by empiric treatment for bacterial meningitis. For patients with risk factors, blood cultures and empiric treatment should begin immediately to prevent delays, as delayed antimicrobial therapy significantly increases mortality and morbidity. One study reported a 21% increase in mortality within a few hours of treatment delay [28–30]. This significant rise in mortality and neurological, among other, sequelae is seen consistently through various studies [31–36].

## TREATMENT

Distinguishing bacterial from nonbacterial meningitis remains a challenge due to variability in clinical presentation, overlapping CSF profiles, and frequent delays in diagnostic results, with Gram staining often negative [8–10].

A recently developed risk score helps differentiate bacterial meningitis from viral meningitis or encephalitis in adults presenting with CSF leukocytosis ( $>10$  cells/ $\mu$ l) and a negative Gram stain. The score includes six variables: fever ( $\geq 38^\circ\text{C}$ ), serum leukocyte count more than 10 000/ $\mu$ l, CSF leukocyte count more than 2000/ $\mu$ L, CSF granulocyte count more than 1180/ $\mu$ l, CSF glucose less than 34 mg/dl, and CSF protein more than 220 mg/dl. Patients with a score of 0 are classified as low risk, while scores more than 0 indicate high risk for bacterial meningitis. In the U.S. derivation cohort, the score demonstrated 100% sensitivity and 34% specificity, and in the Dutch validation cohort, sensitivity was 99.6% with specificity of 41.2% [37]. With its high sensitivity, the score serves as a reliable rule-out test for bacterial meningitis, supporting discontinuation of antibiotics in low-risk patients.

In suspected community-acquired bacterial meningitis in individuals beyond the neonatal age, dexamethasone [0.15 mg/kg intravenous (i.v.)] should be included in the empiric treatment regimen, administered before or concurrently with antimicrobials, and continued for 2–4 days. In adults, dexamethasone reduces mortality in cases caused by *Streptococcus pneumoniae*, while in children, it decreases the risk of hearing loss from *Haemophilus influenzae* type b infections [38]. Once bacterial meningitis is ruled out, adjunctive steroids and antibiotics can be discontinued.

## CAUSES OF ASEPTIC MENINGITIS

### Viral causes

Viral infections, mainly enteroviruses, cause up to 55% of aseptic meningitis cases, peaking in summer and fall [39]. Symptoms include fever, headache, nausea, photophobia, and meningismus, with CSF showing lymphocytic pleocytosis and normal glucose [40]. PCR testing is highly sensitive and specific, while management focuses on supportive care [20].

Herpesviridae are major causes of viral meningitis worldwide, occurring year-round, with HSV-2 being the most common, especially in young females [39,41<sup>□</sup>]. HSV-2 is also responsible for benign lymphocytic meningitis, or Mollaret meningitis. Approximately 50% of HSV-2 meningitis patients report a history of genital lesions, and 30% have prior episodes of HSV meningitis. However, only 8% present with active lesions during the meningitis episode, so their absence should not exclude the diagnosis [41<sup>□</sup>]. The CSF profile resembles that of other viral meningitides. There is no standardized treatment for HSV meningitis, though acyclovir may be more beneficial in immunocompromised individuals [42,43]. Hospitalized patients are typically treated with i.v. acyclovir (10 mg/kg every 8 h) and can transition to oral valacyclovir (1 g every 8 h) to complete a 10-day course upon improvement [43]. Suppressing valacyclovir reduces mucocutaneous lesions but does not prevent meningitis recurrence, so it is not recommended for this purpose [44]. HSV-1 can also cause meningitis but more commonly presents as encephalitis, where it is the leading cause, particularly in adults.

Varicella-zoster virus (VZV) can cause meningitis with or without a vesicular rash, often underdiagnosed due to limited routine PCR testing, with only 1.2% of patients reportedly receiving this diagnostic evaluation [45]. When meningitis occurs without a rash, it is termed *zoster sine herpette*. Treatment mirrors that for HSV meningitis, using i.v. acyclovir (10–15 mg/kg every 8 h) for 10–14 days [46]. Unlike HSV meningitis, transitioning to an oral regimen during therapy is not recommended. VZV is also a less common cause of encephalitis [47<sup>□</sup>].

Cytomegalovirus (CMV) can cause meningitis, encephalitis, myelitis, polyradiculopathy, or retinitis, though encephalitis is more common and primarily affects immunocompromised individuals, particularly those with AIDS and CD4<sup>+</sup> cell counts less than 50 cells/ $\mu$ l. CMV CNS disease is extremely rare and has become even less common with the widespread use of potent antiretroviral therapy [48].

Epstein-Barr virus (EBV) infection, whether primary or reactivated in immunocompromised individuals, has been linked to a range of neurological

conditions, including encephalitis, meningitis, acute disseminated encephalomyelitis, cerebellitis, multiple sclerosis, and CNS lymphomas [49].

Human herpesvirus 6 (HHV-6) is most commonly linked to posttransplant acute limbic encephalitis (PALE) in bone marrow transplant recipients or, less commonly, in patients undergoing CAR T-cell therapy. A positive HHV-6 result in CSF may reflect active infection, viral reactivation, or chromosomal integration, with true infections typically occurring in severely immunosuppressed individuals when no other diagnosis is evident [50]. Additionally, HHV-7 and HHV-8 can occasionally cause encephalitis in immunosuppressed patients, such as those with AIDS or solid organ transplants [51].

Arboviruses, such as West Nile virus (WNV), are endemic in the U.S., with peak incidence in summer and fall. In 2020, the CDC reported 884 arboviral cases, including 731 from WNV, 88 from La Crosse virus, 21 from Powassan virus, 16 from St. Louis encephalitis, 13 each from eastern equine encephalitis and Jamestown Canyon virus, and 2 from unspecified California serogroup viruses [52]. WNV can present with fever, maculopapular rash, and flaccid paralysis in severe cases [52]. CSF findings are consistent with other viral infections. Diagnosis primarily relies on serologic IgM testing, which is usually detectable around day 8 after symptom onset, with CSF IgM often positive earlier [53]. PCR testing, while available, is generally not recommended due to the short duration of viremia, which typically resolves before patients seek care, limiting its sensitivity. However, PCR may be useful for immunocompromised individuals, as viremia can persist longer in this population [54].

See Table 1 for a rapid overview of viral causes of aseptic meningitis.

### BACTERIAL CAUSES OF ASEPTIC MENINGITIS

As noted earlier, classic bacterial meningitis may appear “aseptic” in partially treated cases. Furthermore, some microorganisms are inherently difficult to diagnose due to limitations in conventional diagnostic methods.

### TUBERCULOUS MENINGITIS

CNS tuberculosis (TB) can present as meningitis, tuberculomas, or abscesses. Meningitis, accounting for 5% of extrapulmonary TB cases, typically involves the basilar meninges and cisterns, often visible on MRI with enhancement and associated hydrocephalus or cranial nerve dysfunction. Diagnosis requires high clinical suspicion and does not

**Table 1.** Viral causes of aseptic meningitis

| Cause                                                   | Key features                                                                                      | Diagnostic tests                                                                            | Treatment                                                                                                      | Prevalence                               |
|---------------------------------------------------------|---------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|------------------------------------------|
| Enteroviruses [20,39,40]                                | Most common cause; fecal-oral transmission; predominant in summer and fall                        | PCR with high sensitivity (96%) and specificity (99%)                                       | Supportive care                                                                                                | Most common (up to 55% of viral cases)   |
| Herpesviruses [41 <sup>■</sup> ,42–46,47 <sup>■</sup> ] | HSV-1/2: +/-genital lesions, Mollaret meningitis; VZV: rash or zoster sine herpete (without rash) | PCR for HSV (Se: 98.9%, Sp: 97.1%), VZV (Se: 99%, Sp: 98%)                                  | i.v. acyclovir (10–15 mg/kg Q8H) for 10–14 days; oral step-down valacyclovir in HSV; no oral step-down for VZV | Common (HSV-2 more common than HSV-1)    |
| Arboviruses [52–54]                                     | Seasonal outbreaks; mosquito-borne (e.g., West Nile virus); encephalitis, flaccid paralysis       | IgM serology (Se: 80–95%, Sp: 97–100%); PCR (low sensitivity due to short viremia); CSF IgM | Supportive care                                                                                                | Rare but seasonal                        |
| Cytomegalovirus (CMV) [48]                              | Seen in immunocompromised patients; AIDS (CD4 <sup>+</sup> <50); encephalitis or retinitis        | PCR (Se: 90%, Sp: 97%), antigen testing, or culture                                         | Ganciclovir or foscarnet                                                                                       | Uncommon, primarily in immunocompromised |
| Epstein-Barr Virus (EBV) [49]                           | Neurological involvement, encephalitis, posttransplant complications                              | PCR (Se: 85–90%, Sp: 95–99%); serology                                                      | Supportive care                                                                                                | Rare, often in immunocompromised         |
| Human Herpesvirus 6 (HHV-6) [50,51]                     | Posttransplant acute limbic encephalitis, immunosuppressed hosts                                  | PCR (Se: 85–95%, Sp: 98–99%); serology                                                      | Ganciclovir or foscarnet for severe cases                                                                      | Rare, often in transplant recipients     |

depend on active pulmonary TB. CSF findings include lymphocytic pleocytosis, elevated protein, very low glucose, and increased opening pressure [55]. Acid-fast bacilli staining is positive in approximately 20% of cases, with improved yield from repeated samples, while culture remains the diagnostic gold standard [56]. Molecular tests, such as PCR for MTB DNA, show variable sensitivity depending on prior therapy and clinical criteria, sometimes as low as 5% [55]. The Lancet criteria can help differentiate MTB meningitis from other causes but has limited sensitivity (~50%) and a specificity of about 90% [57].

## SPIROCHETAL MENINGITIS

Lyme meningitis, caused by *Borrelia burgdorferi*, peaks in late summer and early fall in tick-endemic regions. It typically presents with fever, headache, photophobia, and sometimes erythema migrans or facial palsy. By the time meningitis develops, nearly all patients test positive serologically, with high sensitivity and specificity using the two-tier testing approach [58]. CSF analysis usually shows mononuclear pleocytosis, low glucose, and elevated protein levels. While CSF antibody testing is available, it is poorly sensitive. Similarly, CSF PCR testing has

low sensitivity and is not recommended [58]. Guidelines recommend Ceftriaxone 2 g every daily for up to 28 days [58].

Symptomatic syphilitic meningitis, caused by *Treponema pallidum*, typically occurs within 12 months of infection but can arise at any stage of syphilis. A history of high-risk sexual practices is a key diagnostic clue [59]. The rapid plasma reagin (RPR) test is usually positive in these cases. The CSF Venereal Disease Research Laboratory (VDRL) test, while highly specific (>90%), has limited sensitivity (~50%) [60]. CSF PCR testing, though not FDA-approved, has demonstrated sensitivity and specificity of approximately 68 and 92%, respectively [61]. The treatment of choice is i.v. penicillin G for 10–14 days. Although treatment failures are rare, regular RPR titer monitoring is necessary, and in some cases, a repeat lumbar puncture with CSF VDRL monitoring may be needed to confirm treatment success [62].

Leptospira meningitis typically occurs during the immune phase of the disease. CSF analysis may reveal either lymphocytic or neutrophilic predominance, mildly elevated protein levels, and usually normal glucose, though glucose levels can occasionally be slightly reduced [63]. It remains debated whether these findings result from an

**Table 2.** Bacterial causes of aseptic meningitis

| Cause                                                            | Key features                                                                                             | Diagnostic tests/Scores                                                                                                 | Treatment                                                                                      | Prevalence                              |
|------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|-----------------------------------------|
| Bacterial (partially treated) [8–10,16,17,37 <sup>***</sup> ,38] | Indolent course; mimics viral meningitis; lymphocytic or neutrophilic predominance with sterile cultures | CSF culture (Se: 50–90%, Sp: 100%), Gram stain (Se: 10–90%, Sp: 100%), PCR; BioFire multiplex panels (Se: 90%, Sp: 97%) | Empiric antibiotics (e.g., ceftriaxone, vancomycin); dexamethasone pending bacterial exclusion | Uncommon; often due to pretreated cases |
| Tuberculosis [56,57]                                             | Basilar meningitis; hydrocephalus; cranial nerve palsies                                                 | AFB stain (Se: 20–40%, Sp: 100%), culture (Se: 50%), PCR (Se: 60–80%, Sp: 95–100%); Lancet criteria                     | RIPE therapy (Rifampin, Isoniazid, Pyrazinamide, Ethambutol) + corticosteroids                 | Rare, more common in endemic areas      |
| Lyme [58]                                                        | Tick exposure; erythema migrans; cranial nerve palsy                                                     | Serologies (two-tier testing Se: 75–95%, Sp: 99%); CSF analysis (low sensitivity of PCR ~10–30%)                        | Ceftriaxone 2 g i.v. daily for 14–28 days                                                      | Uncommon, endemic areas                 |
| Syphilis [59–62]                                                 | High-risk sexual behavior; cranial nerve palsy, headache                                                 | CSF VDRL (Sp: >90%, Se: ~50%); serologic testing; PCR. Lancet Criteria.                                                 | i.v. Penicillin G for 10–14 days                                                               | Rare, linked to sexual exposure         |
| Leptospira [63,64]                                               | Travel or water exposure; flu-like symptoms; conjunctival suffusion                                      | Serologies (MAT Se: 92–96%, Sp: 98–100%); PCR (Se: 75–85%, Sp: 97–100%).                                                | Doxycycline or penicillin                                                                      | Rare, tropical, and flood-exposed areas |

immune response to systemic illness or direct microbial invasion of the CNS [64].

See Table 2 for a rapid overview of bacterial causes of aseptic meningitis.

## FUNGAL CAUSES

Fungal meningitis is most commonly caused by *Cryptococcus*, *Coccidioides*, and *Histoplasma*, primarily affecting immunocompromised individuals, though immunocompetent hosts in endemic areas may also be at risk.

*Cryptococcus*, primarily *Cryptococcus neoformans* and *Cryptococcus gattii*, is an encapsulated yeast found in soil contaminated with bird droppings. Infection typically occurs via inhalation, leading to pulmonary involvement before hematogenous spread to the CNS. *Cryptococcus* is the leading cause of fungal meningitis worldwide, particularly in patients with HIV/AIDS, solid organ transplants, and those on immunosuppressive therapy. Clinically, it presents with headache, fever, nausea, altered mental status, and cranial nerve palsies. Opening pressure is significantly elevated [65].

*Coccidioides immitis* and *Coccidioides posadasii* are dimorphic fungi endemic to the Southwestern United States and Mexico. Infection occurs via inhalation of airborne arthroconidia. While most cases are asymptomatic or limited to pulmonary symptoms, hematogenous spread can result in

coccidioidal meningitis. Symptoms include headache, photophobia, back pain, and encephalopathy. Basilar meningitis may cause hydrocephalus or cerebral infarcts [66].

*Histoplasma capsulatum* is a dimorphic fungus found in soil contaminated with bird or bat droppings, particularly in the Ohio and Mississippi River Valleys. Infection occurs via inhalation of spores, often leading to pulmonary symptoms. Dissemination to the CNS can result in chronic meningitis, presenting with headache, cranial neuropathies, seizures, and encephalopathy [67].

Diagnosis requires CSF analysis, which often shows a lymphocytic pleocytosis, elevated protein, and low glucose. Specific tests include

- (1) *Cryptococcus*: CSF antigen tests (e.g., lateral flow assay) show 99.3% sensitivity and 99.1% specificity. CSF culture has 82.4–94.2% sensitivity and 100% specificity, while India ink staining is less sensitive (42–86%) but highly specific (97.3%) [65].
- (2) *Coccidioides*: CSF antigen testing is highly sensitive (93%) and specific (100%). IgG EIA serology offers 85% sensitivity and 99% specificity, while CSF cultures have low sensitivity (7–30%) but 100% specificity [66].
- (3) *Histoplasma*: Urine antigen tests are highly sensitive (71–100%) and specific (99%), with higher sensitivity in immunocompromised patients.

**Table 3.** Fungal and parasitic causes of aseptic meningitis

| Cause                                                                   | Key features                                                                        | Diagnostic tests                                                                                            | Treatment                                                               | Prevalence                              |
|-------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|-----------------------------------------|
| Cryptococcus [65]                                                       | Immunocompromised hosts; headaches, altered mental status; high opening pressure    | CSF antigen testing (Se: 99.3%, Sp: 99.1%); India ink stain (Se: 42–86%, Sp: 97.3%); culture                | Amphotericin B + flucytosine induction; fluconazole maintenance therapy | Common in HIV/AIDS, transplant patients |
| Coccidioides [66]                                                       | Endemic regions (Southwestern U.S.); basilar meningitis; hydrocephalus              | CSF antigen testing (Se: 93%, Sp: 100%); IgG/IgM serology (Se: 85%, Sp: 99%); culture (Se: 7–30%, Sp: 100%) | Fluconazole; intrathecal amphotericin B in refractory cases             | Rare, endemic regions                   |
| Histoplasma [67]                                                        | Ohio and Mississippi River Valleys; chronic meningitis                              | CSF antigen (Se: 38–67%, Sp: 96%), urine antigen (Se: 71–100%, Sp: 99%); culture                            | Amphotericin B followed by itraconazole maintenance                     | Rare, endemic to certain regions        |
| Parasitic (Angiostrongylus, Gnathostoma, Baylisascaris, Taenia) [69–71] | Travel to endemic areas; eosinophilic pleocytosis; contaminated food/water exposure | CSF eosinophilia (>10% or $\geq 10$ cells/ $\mu$ l); serology, imaging                                      | Variable                                                                | Rare in USA, linked to travel exposure  |

CSF antigen tests have 38–67% sensitivity and 96% specificity, while antibody tests offer 80–89% sensitivity and 83% specificity [67].

Imaging can reveal hydrocephalus, leptomeningeal enhancement, or granulomatous lesions.

Treatment depends on the pathogen. *Cryptococcus* is treated with amphotericin B and flucytosine, followed by fluconazole maintenance therapy. *Coccidioides* meningitis is treated with fluconazole. *Histoplasma* is treated with amphotericin B followed by itraconazole maintenance [65–67].

Additionally, rarer causes of fungal meningitis, such as *Aspergillus*, *Candida*, *Fusarium*, and *Mucor*, exist. In these cases, emerging evidence suggests that (1→3)- $\beta$ -D-glucan in CSF may serve as a useful biomarker for invasive fungal diseases of the CNS, particularly for *Candida* and *Aspergillus* infections [68].

See Table 3 for a rapid overview of fungal causes of aseptic meningitis.

## PARASITIC CAUSES

Parasitic eosinophilic meningitis is characterized by CSF findings that include eosinophilia exceeding 10% (or  $\geq 10$  cells/ $\mu$ l), elevated protein levels, and normal to low glucose concentrations. Generally, diagnosis relies on a proper history taking, serology and exclusion of other causes, with brain biopsy reserved for inconclusive cases.

The most common parasitic etiology is *Angiostrongylus cantonensis* (rat lungworm), which is endemic in Southeast Asia, the Pacific Basin, and

parts of the Caribbean. Humans become infected through consumption of raw snails, contaminated vegetables, or intermediate hosts like freshwater shrimp. The larvae migrate to the CNS, triggering an inflammatory response that leads to eosinophilic meningitis. Clinical symptoms include headache, neck stiffness, visual disturbances, and paresthesias [69–71].

Helminths linked to eosinophilic meningitis include *Gnathostoma spinigerum*, *Baylisascaris procyonis*, and *Taenia solium*. *Gnathostoma spinigerum*, endemic in Southeast Asia and Latin America, is acquired through undercooked fish or poultry, causing radiculitis, nerve pain, and CNS involvement through larval migration, which may lead to hemorrhagic tracks and focal lesions detectable on MRI [71]. *Baylisascariasis*, linked to raccoons, is contracted through ingestion of eggs in contaminated soil. The larvae invade the CNS, causing meningoencephalitis with diffuse white matter lesions. *Taenia solium* causes neurocysticercosis where humans become infected by ingesting eggs from contaminated food or water. The larvae migrate to the CNS, forming cysts that trigger inflammation, presenting with headache, neck stiffness, and cranial nerve palsies. Imaging can reveal cysts in the ventricles or subarachnoid spaces [69,70]. Neurocysticercosis can mimic tuberculous meningitis, complicating diagnosis [70].

While parasitic eosinophilic meningitis is rare in North America, international travel and global migration increase the risk of exposure.

See Table 3 for a rapid overview of viral causes of parasitic meningitis.

**Table 4.** Noninfectious causes of aseptic meningitis

| Cause                                    | Key Features                                                                         | Diagnostic tests                                                                                        | Treatment                                            | Prevalence                            |
|------------------------------------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|------------------------------------------------------|---------------------------------------|
| Drug-induced [74,75]                     | Temporal relation to drug exposure; NSAIDs, antibiotics, IVIG, monoclonal antibodies | Diagnosis of exclusion; CSF pleocytosis (lymphocytic or neutrophilic); elevated protein, normal glucose | Discontinuation of offending drug; supportive care   | Uncommon, associated with medications |
| Neoplastic [72]                          | Cancer history; CNS symptoms (headache, seizures, cranial nerve palsies)             | CSF cytology (Se: ~50%, Sp: 100%), flow cytometry, MRI with gadolinium                                  | Intrathecal chemotherapy, radiation, palliative care | Rare, linked to malignancies          |
| Autoimmune (e.g., SLE, Sarcoidosis) [73] | Neurological signs; uveitis, arthritis, other systemic signs                         | CSF pleocytosis, MRI with enhancement; antibody testing                                                 | Corticosteroids, immunosuppressive therapy           | Rare, linked to autoimmune diseases   |
| Idiopathic                               | No identifiable cause despite extensive workup                                       | Diagnosis of exclusion; CSF analysis, imaging                                                           | Supportive care                                      | Common, up to 50% of cases            |

## NON-INFECTIOUS CAUSES

Neoplastic meningitis, the infiltration of leptomeninges by malignant cells, occurs in approximately 5% of cancer patients, particularly those with breast or lung cancers, melanoma, leukemia, or lymphoma. Neoplastic meningitis spreads hematogenously, by direct extension, or via perineural or perivascular migration, causing significant morbidity and a poor prognosis [72]. Symptoms include headache, mental status changes, seizures, cranial nerve palsies, and spinal cord dysfunction (e.g., weakness, sensory loss). Diagnosis is based on CSF analysis, typically showing increased opening pressure, lymphocytic pleocytosis, elevated protein, and low glucose. Confirmation requires detecting malignant cells via cytology or flow cytometry, which are highly specific but variably sensitive, sometimes requiring a direct meningeal biopsy unless systemic neoplastic disease supports a presumptive diagnosis [72]. MRI with gadolinium can reveal leptomeningeal enhancement, cranial nerve involvement, and intradural or extramedullary nodules.

Systemic inflammatory disorders (SIDs), such as sarcoidosis, Behçet's disease, and systemic lupus erythematosus, can present as acute aseptic meningitis, sometimes as the initial manifestation. Both neurological and extraneurological signs are critical for distinguishing SID-related meningitis [73]. Neurological symptoms include focal deficits, seizures, and delirium, while extraneurological signs like uveitis, arthralgia, and skin lesions aid diagnosis. CSF analysis typically reveals elevated protein, low glucose, and lymphocytic pleocytosis. MRI may reveal T2-weighted high-signal lesions, pseudotumoral changes, or myelitis. Corticosteroids typically result in clinical improvement [73].

Drug-induced aseptic meningitis (DIAM) is a noninfectious meningeal inflammation caused by medications, through direct irritation (e.g., intrathecal drugs) or hypersensitivity reactions to systemic drugs. Symptoms mimic infectious meningitis, making diagnosis reliant on exclusion and temporal drug exposure. CSF analysis shows pleocytosis (neutrophilic or lymphocytic), elevated protein, and normal glucose [74,75]. DIAM involves hypersensitivity, immune complex formation, or cytotoxicity, with autoimmune conditions like SLE increasing susceptibility. Common culprits include NSAIDs, antibiotics (e.g., trimethoprim-sulfamethoxazole), immunotherapies (IVIG, mAbs), anticonvulsants (lamotrigine, carbamazepine), and vaccines (e.g., MMR) [74,75]. Management of DIAM involves discontinuing the offending drug, which usually leads to rapid symptom resolution within two to three days, with full recovery expected [75].

See Table 4 for a rapid overview of noninfectious causes of aseptic meningitis.

## CONCLUSION

Aseptic meningitis has various infectious and non-infectious causes, some requiring urgent treatment for survival. Most cases, however, are viral, with patients often admitted and started on empirical antibiotics. Clinical models and rapid PCR testing can help identify viral causes, reducing antibiotic use, hospital stays, and associated costs.

## Acknowledgements

None.

## Financial support and sponsorship

None.

## Conflicts of interest

RH has received research funding and personal fees from Biomerieux.

## REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Wallgren A. A new infectious disease of the central nervous system? *Acta Padiatr* 1925; 4:158–182.
2. Gundamraj V, Hasbun R. Viral meningitis and encephalitis: an update. *Curr Opin Infect Dis* 2023; 36:177–185.
- A comprehensive review of the most common causes of viral meningitis and encephalitis.
3. Bijlsma MW, Brouwer MC, Kasanmoentalib ES, *et al.* Community-acquired bacterial meningitis in adults in the Netherlands, 2006–14: a prospective cohort study. *Lancet Infect Dis* 2016; 16:339–347.
4. Bystritsky RJ, Chow FC. Infectious meningitis and encephalitis. *Neurol Clin* 2022; 40:77–91.
5. Brody IA, Wilkins RH. The signs of Kernig and Brudzinski. *Arch Neurol* 1969; 21:215–216.
6. Thomas KE, Hasbun R, Jekel J, Quagliarello VJ. The diagnostic accuracy of Kernig's Sign, Brudzinski's Sign, and nuchal rigidity in adults with suspected meningitis. *Clin Infect Dis* 2002; 35:46–52.
7. Iguchi M, Noguchi Y, Yamamoto S, *et al.* Diagnostic test accuracy of jolt accentuation for headache in acute meningitis in the emergency setting. *Cochrane Database Syst Rev* 2020; 2020; CD012824.
8. Durand ML, Calderwood SB, Weber DJ, *et al.* Acute bacterial meningitis in adults – a review of 493 episodes. *N Engl J Med* 1993; 328:21–28.
9. Fitch MT, van de Beek D. Emergency diagnosis and treatment of adult meningitis. *Lancet Infect Dis* 2007; 7:191–200.
10. van de Beek D, de Gans J, Spanjaard L, *et al.* Clinical Features and Prognostic Factors in Adults with Bacterial Meningitis. *N Engl J Med* 2004; 351: 1849–1859.
11. Kanegaye JT, Soliemanzadeh P, Bradley JS. Lumbar puncture in pediatric bacterial meningitis: defining the time interval for recovery of cerebrospinal fluid pathogens after parenteral antibiotic pretreatment. *Pediatrics* 2001; 108:1169–1174.
12. Shrikanth V, Salazar L, Khoury N, *et al.* Hypoglycorrhachia in adults with community-acquired meningitis: etiologies and prognostic significance. *Int J Infect Dis* 2015; 39:39–43.
13. Jaijakul S, Salazar L, Wootton SH, *et al.* The clinical significance of neutrophilic pleocytosis in cerebrospinal fluid in patients with viral central nervous system infections. *Int J Infect Dis* 2017; 59:77–81.
14. Thwaites G, Fisher M, Hemingway C, *et al.* British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. *J Infect* 2009; 59:167–187.
15. Mylonakis E, Hohmann EL, Calderwood SB. Central nervous system infection with *Listeria monocytogenes*: 33 years' experience at a general hospital and review of 776 episodes from the literature. *Medicine* 1998; 77:313–336.
16. Leber AL, Everhart K, Balada-Llasat J-M, *et al.* Multicenter evaluation of BioFire FilmArray meningitis/encephalitis panel for detection of bacteria, viruses, and yeast in cerebrospinal fluid specimens. *J Clin Microbiol* 2016; 54:2251–2261.
17. van de Beek D, Brouwer MC, Koedel U, Wall EC. Community-acquired bacterial meningitis. *Lancet* 2021; 398:1171–1183.
18. Tansarli GS, Chapin KC. Diagnostic test accuracy of the BioFire® FilmArray® meningitis/encephalitis panel: a systematic review and meta-analysis. *Clin Microbiol Infect* 2020; 26:281–290.
19. Zanella M-C, Cherkaoui A, Hinic V, *et al.* Unexpectedly high false-positive rates for *Haemophilus influenzae* using a Meningoencephalitis syndromic PCR panel in two tertiary centers. *Front Cell Infect Microbiol* 2021; 11:639658.
20. Lin M, Li Y-R, Lan Q-W, *et al.* Evaluation of GeneXpert EV assay for the rapid diagnosis of enteroviral meningitis: a systematic review and meta-analysis. *Ann Clin Microbiol Antimicrob* 2022; 21:25.
21. Nix WA, Maher K, Pallansch MA, Oberste MS. Parechovirus typing in clinical specimens by nested or semi-nested PCR coupled with sequencing. *J Clin Virol* 2010; 48:202–207.
22. Vaugon E, Mircescu A, Caya C, *et al.* Diagnostic accuracy of rapid one-step PCR assays for detection of herpes simplex virus-1 and -2 in cerebrospinal fluid: a systematic review and meta-analysis. *Clin Microbiol Infect* 2022; 28:1547–1557.
23. Wilson MR, Sample HA, Zorn KC, *et al.* Clinical metagenomic sequencing for diagnosis of meningitis and encephalitis. *N Engl J Med* 2019; 380:2327–2340.
24. Obaro S, Hassan-Hanga F, Medugu N, *et al.* Comparison of bacterial culture with BioFire® FilmArray® multiplex PCR screening of archived cerebrospinal fluid specimens from children with suspected bacterial meningitis in Nigeria. *BMC Infect Dis* 2023; 23:641.
25. Wei T-T, Hu Z-D, Qin B-D, *et al.* Diagnostic accuracy of procalcitonin in bacterial meningitis versus nonbacterial meningitis. *Medicine* 2016; 95: e3079.
26. Vikse J, Henry BM, Roy J, *et al.* The role of serum procalcitonin in the diagnosis of bacterial meningitis in adults: a systematic review and meta-analysis. *Int J Infect Dis* 2015; 38:68–76.
27. Tapiainen T, Prevots R, Izurieta HS, *et al.* Aseptic meningitis: Case definition and guidelines for collection, analysis and presentation of immunization safety data. *Vaccine* 2007; 25:5793–5802.
28. Tunkel AR, Hartman BJ, Kaplan SL, *et al.* Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis* 2004; 39:1267–1284.
29. Salazar L, Hasbun R. Cranial imaging before lumbar puncture in adults with community-acquired meningitis: clinical utility and adherence to the Infectious Diseases Society of America Guidelines. *Clin Infect Dis* 2017; 64:1657–1662.
30. Miner JR, Heegaard W, Mapes A, Biros M. Presentation, time to antibiotics, and mortality of patients with bacterial meningitis at an urban county medical center. *J Emerg Med* 2001; 21:387–392.
31. Bodilsen J, Dalager-Pedersen M, Schønheyder HC, Nielsen H. Time to antibiotic therapy and outcome in bacterial meningitis: a Danish population-based cohort study. *BMC Infect Dis* 2016; 16:392.
32. Køster-Rasmussen R, Korshin A, Meyer CN. Antibiotic treatment delay and outcome in acute bacterial meningitis. *J Infect* 2008; 57:449–454.
33. Proulx N, Fréchette D, Toye B, *et al.* Delays in the administration of antibiotics are associated with mortality from adult acute bacterial meningitis. *CJM* 2005; 98:291–298.
34. Lepur D, Barsić B. Community-acquired bacterial meningitis in adults: antibiotic timing in disease course and outcome. *Infection* 2007; 35: 225–231.
35. Auburtin M, Wolff M, Charpentier J, *et al.* Detrimental role of delayed antibiotic administration and penicillin-nonsusceptible strains in adult intensive care unit patients with pneumococcal meningitis: the PNEUMOREA prospective multicenter study\*. *Crit Care Med* 2006; 34:2758–2765.
36. Aronin SI, Peduzzi P, Quagliarello VJ. Community-acquired bacterial meningitis: risk stratification for adverse clinical outcome and effect of antibiotic timing. *Ann Intern Med* 1998; 129:862–869.
37. van Soest TM, Horst L ter, Chekrouni N, *et al.* A risk score for identifying patients at a low risk of bacterial meningitis amongst adults with cerebrospinal fluid leucocytosis and a negative gram stain result: a derivation and validation study. *Clin Microbiol Infect* 2023; 29:360–365.
- Derivation and validation of a novel risk score to help clinicians differentiate bacterial meningitis from viral central nervous system infections.
38. van de Beek D, Brouwer MC, Koedel U, Wall EC. Steroid use in nonpneumococcal and non-*Haemophilus* bacterial meningitis – authors' reply. *Lancet* 2022; 399:718.
39. Kupila L, Vuorinen T, Vainionpää R, *et al.* Etiology of aseptic meningitis and encephalitis in an adult population. *Neurology* 2006; 66:75–80.
40. Sulaiman T, Salazar L, Hasbun R. Acute versus subacute community-acquired meningitis: analysis of 611 patients. *Medicine* 2017; 96:e7984.
41. Jakobsen A, Skov MT, Larsen L, *et al.* Herpes simplex virus 2 meningitis in adults: a Prospective, Nationwide, population-based cohort study. *Clin Infect Dis* 2022; 75:753–760.
- Largest prospective study evaluating the clinical presentations and outcomes of adults with herpes simplex type 2 meningitis.
42. Noska A, Kyrillos R, Hansen G, *et al.* The role of antiviral therapy in immunocompromised patients with herpes simplex virus meningitis. *Clin Infect Dis* 2015; 60:237–242.
43. Kaewpoowat Q, Salazar L, Aguilera E, *et al.* Herpes simplex and varicella zoster CNS infections: clinical presentations, treatments and outcomes. *Infection* 2016; 44:337–345.
44. Aurelius E, Franzen-Rohl E, Glimaker M, *et al.* Long-term valacyclovir suppressive treatment after herpes simplex virus type 2 meningitis: a double-blind, randomized controlled trial. *Clin Infect Dis* 2012; 54:1304–1313.
45. Shukla B, Aguilera EA, Salazar L, *et al.* Aseptic meningitis in adults and children: diagnostic and management challenges. *J Clin Virol* 2017; 94:110–114.
46. Tunkel AR, Glaser CA, Bloch KC, *et al.* The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2008; 47:303–327.
47. Dulin M, Chevret S, Salmona M, *et al.* New insights into the therapeutic management of Varicella Zoster virus meningitis: a series of 123 polymerase chain reaction-confirmed cases. *Open Forum Infect Dis* 2024; 11:ofae340.
- The largest study evaluating the clinical presentation and management of patients with VZV meningitis.
48. Schwarcz L, Chen M-J, Vittinghoff E, *et al.* Declining incidence of AIDS-defining opportunistic illnesses. *AIDS* 2013; 27:597–605.
49. Andersen O, Ernberg I, Hedström AK. Treatment options for Epstein-Barr virus-related disorders of the central nervous system. *Infect Drug Resist* 2023; 16:4599–4620.

50. Handley G, Hasbun R, Okhuysen P. Human herpesvirus 6 and central nervous system disease in oncology patients: a retrospective case series and literature review. *J Clin Virol* 2021; 136:104740.
51. Mann I, Morado-Aramburo O, Hasbun R. Emerging shadows: HHV-8-associated encephalitis unveiled in a solid organ transplant recipient. *Transplant Infect Dis* 2024; 26:e14343.
52. Hasbun R, Garcia MN, Kellaway J, *et al.* West Nile virus retinopathy and associations with long term neurological and neurocognitive sequelae. *PLoS One* 2016; 11:e0148898.
53. Prince HE, Tobler LH, Lapé-Nixon M, *et al.* Development and persistence of West Nile virus-specific immunoglobulin M (IgM), IgA, and IgG in viremic blood donors. *J Clin Microbiol* 2005; 43:4316–4320.
54. Busch MP, Caglioti S, Robertson EF, *et al.* Screening the blood supply for West Nile Virus RNA by nucleic acid amplification testing. *N Engl J Med* 2005; 353:460–467.
55. Nelson CA, Zunt JR. Tuberculosis of the central nervous system in immunocompromised patients: HIV infection and solid organ transplant recipients. *Clin Infect Dis* 2011; 53:915–926.
56. Süttaş PN, Ünal A, Forta H, *et al.* Tuberculous meningitis in adults: review of 61 cases. *Infection* 2003; 31:387–391.
57. Sulaiman T, Medi S, Erdem H, *et al.* The diagnostic utility of the “Thwaites’ system” and “lancet consensus scoring system” in tuberculous vs. nontuberculous subacute and chronic meningitis: multicenter analysis of 395 adult patients. *BMC Infect Dis* 2020; 20:788.
58. Lantos PM, Rumbaugh J, Bockenstedt LK, *et al.* Clinical Practice Guidelines by the Infectious Diseases Society of America, American Academy of Neurology, and American College of Rheumatology. *Neurology* 2021; 96:262–273.
59. Workowski KA, Bachmann LH. Centers for Disease Control and Prevention’s sexually transmitted diseases infection guidelines. *Clin Infect Dis* 2022; 74: S89–S94.
60. Marra CM, Maxwell CL, Dunaway SB, *et al.* Cerebrospinal fluid treponema pallidum particle agglutination assay for neurosyphilis diagnosis. *J Clin Microbiol* 2017; 55:1865–1870.
61. Marks M, Lawrence D, Kositz C, Mabey D. Diagnostic performance of PCR assays for the diagnosis of neurosyphilis: a systematic review. *Sex Transm Infect* 2018; 94:585–588.
62. Workowski KA, Bachmann LH, Chan PA, *et al.* Sexually transmitted infections treatment guidelines. *MMWR Recomm Rep* 2021; 70:1–187.
63. Helmer RE. Hypoglycorrachia in leptospirosis. *Ann Intern Med* 1973; 79:912.
64. Berman SJ. Sporadic anicteric leptospirosis in South Vietnam. *Ann Intern Med* 1973; 79:167.
65. Abassi M, Boulware DR, Rhein J. Cryptococcal meningitis: diagnosis and management update. *Curr Trop Med Rep* 2015; 2:90–99.
66. Blair JE. Coccidioid meningitis: update on epidemiology, clinical features, diagnosis, and management. *Curr Infect Dis Rep* 2009; 11:289–295.
67. Wheat LJ, Musial CE, Jenny-Avital E. Diagnosis and management of central nervous system histoplasmosis. *Clin Infect Dis* 2005; 40:844–852.
68. Walsh TJ, Zhang SX. Emerging roles of (1→3)- $\beta$ -D-Glucan in cerebrospinal fluid for detection and therapeutic monitoring of invasive fungal diseases of the central nervous system. *Clin Infect Dis* 2024; 78:11–14.
- Evaluation of the CSF 1→3)- $\beta$ -D-Glucan in the patients with central nervous system fungal infections.
69. Re V Lo, Gluckman SJ. Eosinophilic meningitis. *Am J Med* 2003; 114:217–223.
70. Sawanyawisuth K, Chotmongkol V. Eosinophilic Meningitis. In *Handbook of Clinical Neurology*; Elsevier, 2013; 114: 207–215. <https://doi.org/10.1016/B978-0-444-53490-3.00015-7>.
71. Ramirez-Avila L, Slome S, Schuster FL, *et al.* Eosinophilic meningitis due to *Angiostrongylus* and *Gnathostoma* species. *Clin Infect Dis* 2009; 48:322–327.
72. Chamberlain MC. Neoplastic meningitis. *Oncologist* 2008; 13:967–977.
73. de la Motte MB, Abbas R, Jouan F, *et al.* Systemic inflammatory disorders in patients admitted for aseptic meningitis. *Clin Med* 2018; 18:132–137.
74. Yelehe-Okouma M, Czml-Garon J, Pape E, *et al.* Drug-induced aseptic meningitis: a mini-review. *Fundam Clin Pharmacol* 2018; 32:252–260.
75. Bihan K, Weiss N, Théophile H, *et al.* Drug-induced aseptic meningitis: 329 cases from the French pharmacovigilance database analysis. *Br J Clin Pharmacol* 2019; 85:2540–2546.