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Review Article

Viral (aseptic) meningitis: A review

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ABSTRACT

Viral meningitis is an inflammation of the meninges associated with acute onset of meningeal symptoms and fever, pleocytosis of the cerebrospinal fluid, and no growth on routine bacterial culture. It is sometimes associated with viral encephalitis and meningoencephalitis. Viruses reach the central nervous system (CNS) hematogenously or in a retrograde manner from nerve endings. The viral etiology varies according to age and country. Molecular diagnostics technology has helped improve the rate of pathogen detection reducing unnecessary antibiotic use and length of hospitalization. Most of the viral infections detailed in this article have no specific treatment other than supportive care. Many of the viruses discussed are preventable by vaccination and proper skin protection against transmitting vectors.

1. Introduction

Cerebrospinal fluid (CSF) has been recognized since antiquity, as recorded by Egyptian physicians in Ebers papyrus which described the meninges [1]. As early as the 5th century BCE Hippocratic physicians were aware of CSF and hydrocephalus [1]. This understanding took a scientific turn in 1891, when German physician Heinrich Irenaeus Quincke (1842–1922) used various needles and stylets with his "*lumbalpunction*" to remove CSF among children suffering from hydrocephalus [1,2]. Quincke was nominated for the 1909 and 1918 Nobel Prize in physiology or medicine due to his therapeutic and diagnostic work using lumbar punctures [2]. In 1925 Swedish physician Arvid Wallgren (1889–1973) coined the term "*acute aseptic meningitis*" [3]. He presented clinical findings, postulated neurotropic virus pathogens (e.g. poliomyelitis and mumps), and suggested alterations in CSF typical of meningitis as criteria for this syndrome (Table 1) [3]. Subsequently, Rivers and Scott [4] in 1935 isolated the Lymphocytic choriomeningitis virus (LCM) from CSF in two male patients with benign aseptic meningitis and in 1947 Rhodes and Beale [5] presented evidence for Coxsackie virus of Dalldorf's Group B as a cause of benign aseptic meningitis among 100 children.

The term aseptic meningitis encompasses broad differential diagnoses related to inflammation of the meninges not due to pyogenic bacteria. Although viral pathogens are the most common etiology, many different causes – both infective and non-infective – can be responsible for aseptic meningitis. The spectrum of non-infectious causes may include drug-induced (e.g. amoxicillin, nonsteroidal anti-inflammatory medications or trimethoprim-sulfamethoxazole), neoplastic, neurosarcoidosis, rheumatoid arthritis, systemic lupus erythematosus, or vasculitis (e.g. Kawasaki disease) [3]. While the term is not synonymous with viral meningitis, the two are often used interchangeably. Viral meningitis is a common disorder encountered by practicing clinicians to include primary care and emergency physicians, neurologists and neurologic surgeons, pediatricians and infectious diseases specialists. It is important to have a thorough and evidenced-based understanding of this entity to provide appropriate and timely interventions. This article reviews some important causes, clinical and epidemiologic features, diagnostic approaches, and management considerations for patients with viral meningitis.

2. Classification and epidemiology

Viral infection of the central nervous system (CNS) produces inflammation in distinct anatomical regions such as the meninges, brain parenchyma, and cranial nerves or in simultaneously multiple regions (Box 1) [6–10]. While inflammation isolated to the meninges produces meningitis, involvement of the brain parenchyma results in encephalitis. Pathologically there may be an inflammatory continuum between these adjacent anatomic regions known as meningoencephalitis.

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Table 1
Wallgren's criteria for the syndrome aseptic meningitis.
Adapted from Adair CV, et al. Ann Intern Med. 1953 Oct;39(4):675–704.

1.Acute onset of symptoms and signs of meningeal involvement
2.Alteration of cerebrospinal fluid typical of meningitis
3.Absence of bacteria in cerebrospinal fluid
4.Relatively short benign course of illness
5.Absence of local parameningeal infection in which meningitis may present as a secondary manifestation
6.Absence of epidemic disease of which meningitis is a feature

Based upon the Centers for Disease Control and Prevention's case definition (Table 2), population-based estimates in the United States have suggested an overall incidence for enteroviral meningitis of 8–10 per 100,000 persons among all ages [11,12]. From the years of 1988 through 1999 viral meningitis was estimated to account for an average hospitalization rate of 36,000 persons per year (14 per 100,000 population), resulting in an annual estimated cost of USD 234–310 million [13]. Viral meningitis exhibits a summer-to-fall seasonality in temperate climates and a year-round incidence in tropical and subtropical areas [11,12,14–16] with causative pathogens primarily transmitted through fecal-oral contamination, and less commonly in respiratory secretions [11–19].

Non-polio human enteroviruses (NPEV) are the leading recognizable cause of viral meningitis accounting for 23% to 61% of cases in which a pathogen is identified (Table 3) [15–19]. Human enteroviruses belong to the *Picornaviridae* family and are characterized by a single positive-strand ribonucleic acid (RNA) genome encoding a polyprotein post-translationally cleaved to yield four structural proteins (VP1-4) and seven non-structural proteins (2A-C and 3A-D) [20,21]. Currently > 110 genetically distinct enteroviruses have been identified and taxonomically placed into four species (Table 4) [20,21]. With a worldwide distribution and humans as the only natural reservoir, the majority of meningitis cases are due to Enterovirus species B, particularly echovirus 6 and 30 [11,22–27]. Other less common viruses include: Echovirus 9, 13, 14, and 16 (species B), Echovirus A71 (species A), and Coxsackievirus A9 and B5 (species B) [11,25–27].

Mumps virus, a member of the family *Paramyxoviridae*, is another leading recognizable cause of viral meningitis accounting for 7.5% to 15.8% of cases [3,15,17]. The virus is an enveloped particle containing a non-segmented negative strand RNA molecule encapsidated by a genome containing tandemly linked transcription units, particularly fusion (F) and haemagglutinin-neuraminidase (HN) proteins thought to mediate cell-to-cell membrane fusion and viral spread through the choroid plexus [28,29]. Currently there are 12 genotypes (designated A-N; excluding E and M) with the majority of meningitis cases due to genotypes B and G [30–32]. The virus is highly neurotropic with vaccination providing limited protection [32]; however, cases have been reported in patients vaccinated from inadequately attenuated strains [33] and in individuals coinfected with enteroviruses, particularly echovirus 30 [34].

Lymphocytic choriomeningitis virus (LCMV), a member of the family *Arenaviridae*, is an unusual rodent-borne pathogen, primarily transmitted by the house mouse (*Mus musculus*), recognized as a cause of viral meningitis accounting for 1.9% to 9.7% of cases in older series [3,15,17,35–37]. While human infection occurs most commonly from winter through early spring by inhalation of aerosolized urine and droppings of infected rodents (e.g. house mouse, hamster and guinea pigs), transmission has also been reported by vertical transmission, and among corneal, liver and kidney organ transplant recipients [3,15,17,35–38]. Based upon comparison of small (S) RNA genomes, LCMV is divided into four main lineages (roman numerals I–IV) with most infections due to lineage I pathogens [35,36].

Herpes simplex viruses (HSV), a member of the family *Herpesviridae*, have accounted for approximately 0.5% to 18% of viral meningitis cases in older series [3,15–17]. While HSV type 1 (HSV-1) has been the most commonly identified cause of sporadic encephalitis worldwide, HSV type 2 (HSV-2) is associated with benign recurrent aseptic meningitis and recurrent benign lymphocytic meningitis (RBLM) [39–41]. HSV-2 is a common sexually transmitted infection (STI) associated with oral and genital mucocutaneous lesions with an estimated seroprevalence of 10–25% [39]. The double-stranded deoxyribonucleic acid (DNA) virus is neurotropic and usually colonizes the sacral sensory ganglia during the latent period following primary infection [39]. Meningitis usually occurs without genital lesions or a prior genital herpes infection history [39]. Among 665 patients treated for Lymphocytic meningitis, Kallio-Laine and colleagues reported a prevalence of HSV-2 associated meningitis of 2.2/100,000 population [39]. RBLM is estimated to occur in 20–30% of cases following primary HSV-2 meningitis [39–41].

Other forms of viral meningitis (Table 5) beyond those caused by the above mentioned, albeit at much lower rates, include the arthropod-borne (transmitted primarily through the bite of an infected mosquito or tick) flaviviruses, bunyaviruses, and orthobunyavirus (especially West Nile virus (WNV), Zika virus, Chikungunya virus, Dengue virus (DENV), La Crosse virus, Jamestown Canyon virus, St. Louis encephalitis virus, Powassan virus, Eastern equine encephalitis virus, and Cache Valley virus) and various members of the herpesvirus family (varicella-zoster virus (VZV), and human herpesvirus type 6 (HHV6)) [14,40,42–44]. Among human immunodeficiency virus (HIV)-infected populations viral pathogens may include other members of the herpesvirus family (Epstein–Barr virus (EBV), cytomegalovirus (CMV), and varicella zoster virus (VZV)) well as members of the polyomavirus family, especially the John Cunningham (JC) virus [45].

3. Pathogenesis

Although the central nervous system (CNS) is protected by a highly complex barrier system, viral pathogens are able to establish infection in cerebral vascular endothelial cells, which allow direct passage across the blood brain barrier (BBB) to adjacent glia and neurons (Fig. 1) [6–10]. Additionally, several other mechanisms include direct infection of the choroid plexus epithelium (e.g. Mumps virus), viral infected hematopoietic cells transported to the CNS by direct blood flow, or lymphoid tissue or inflammation-induced breakdown of the BBB [6,9,28,29,46,47]. Alternatively, viral pathogens may infect and migrate to the CNS through peripheral sensory or motor neurons or olfactory sensory neurons whose dendrites are directly exposed to nasal airways [9,39,46,47]. In general, viruses that target cells of the meninges or ventricular lining, choroid plexus and ependymal often induce meningitis, whereas those that infect the CNS parenchyma give rise to meningoencephalitis, encephalitis, or myelitis.

Once viral tropism allows passage to the CNS, infection is characterized by release of chemoattractants in the meninges followed by an ensuing innate immune cell infiltration of neutrophils, monocytes and antiviral CD8 lymphocytes [6,7,9]. In a murine model of viral meningitis due to LCMV, researchers demonstrated elevated CSF levels of interleukin (IL) -6 and interferon (INF) -gamma [48]. While IL-6 CSF levels began to rise significantly within 24 h after infection, INF-gamma levels were not detected until 5–6 days after infection [48]. CNS concentrations of IL-6 were also found to be elevated during the initial 48 h of enterovirus 71 infection [49]. Among patients with culture-proven enteroviral meningitis the meningeal inflammatory cascade has also included elevated levels of tumor necrosis factor alpha (TNF-alpha) and interleukin 1 beta (IL-1 beta) [50]. An intact host cell-mediated immune response, particularly T-cells, is important for clearance of viruses from the CNS [6,7,9].

Box 1
Classification and definitions.

Encephalitis - Inflammation of the brain parenchyma; cerebral cortex disease causing altered mental status and focal or diffuse neurological signs.

Meningitis - Inflammation of the meninges associated with acute onset of meningeal symptoms and fever, pleocytosis of the cerebrospinal fluid, and no growth on routine bacterial culture.

Meningoencephalitis - Central nervous system infection with clinical features of both meningeal and parenchymal disease.

Table 2
Centers for Disease Control and Prevention (CDC) case definition of viral meningitis.
Adapted from Case definitions for infectious conditions under public health surveillance. Centers for Disease Control and Prevention. MMWR Recomm Rep. 1997 May 2;46(RR-10):1–55.

Clinical criteria: A patient with acute onset of meningeal symptoms and fever
Laboratory criteria: Cerebrospinal fluid (CSF) pleocytosis without culture or serological evidence of a bacterial or mycotic microorganism

4. Clinical features

4.1. Non-polio human enteroviruses (NPEV)

Clinical disease observed in patients with enteroviral meningitis depends upon the host age and immune state (Table 6) [14,19,51–56]. The most frequent manifestations among adults were headache (97–100%), photophobia (79–85%), fever > 38 °C (65–83%), nausea and vomiting (50–76%), and neck stiffness (55–69%) [14,54–56]. Headache peaks around day two of illness and is described as "throbbing" in as many as 65% of cases [14,54]. Gastrointestinal symptoms of generalized abdominal pain and diarrhea occurs in approximately 5–17% of cases anywhere from one week to one day prior to the onset of meningitis symptoms [14,55,56]. Coxsackie and Echo viruses may be associated with a maculopapular, nonpruritic rash commonly involving the face and trunk [14,51,52,54–56]. Other clues to the presence of enterovirus infection include painful vesicles on the posterior oropharynx (Coxsackievirus A), known as *Herpangina*, and pericarditis or pleurisy (Coxsackievirus B) [52,54]. Most patients recover from illness within 7–18 days without sequelae [14,54–56].

4.2. Lymphocytic choriomeningitis virus (LCMV)

Predominant symptoms and signs associated with LCMV include headache (98–100%), neck stiffness (67–91%), and fever (89–98%) lasting an average of 5–6 days [3,35–37]. A prodromal influenza-like illness occurring an average of ten days prior to the onset of meningitis may occur in as many as 30–40% of cases [3]. Additional manifestations associated with meningitis include nausea and vomiting (65–100%), arthralgias and myalgias (56–67%), abdominal pain and diarrhea (8–67%), and photophobia (19%) [3,35–37]. Historically seen as a sequela of encephalitis, Parkinsonism following LCMV meningitis

Table 4
Current human enterovirus taxonomy.
Adapted from: Lugo and Krogstad. Curr Opin Pediatr. 2016 February; 28(1): 107–113.

Enterovirus species	Viral subtypes
A	Coxsackievirus 1–8, 10, 12, 14, 16 Enterovirus A71, A76, A89, A90, A114, A119, A120, A121
B	Coxsackie B 1–6, A9 Echovirus 1–7, 9, 11–21, 24–27, 29–33 Enterovirus B 69, 73–75, 77–88, 93, 97–98, 100, 101, 106–107
C	Coxsackie virus A1, 11, 13, 17, 19, 20, 21, 22, 24 Enterovirus C 95–96, 99, 102, 104–105, 109, 113, 116–118 Poliovirus 1–3
D	EVD68, D70, D94, D111

Table 5
Etiology of viral meningitis.

Common viruses[a]	Uncommon viruses[b]
Non-polio human enteroviruses (NPEV)	Cache valley virus
Coxsackievirus	Chikungunya virus
Echovirus	Cytomegalovirus (CMV)
Enterovirus	Dengue virus
Herpes simplex virus (HSV)	Eastern equine encephalitis virus
HSV type 1	Epstein-Barr virus (EBV)
HSV type 2	Human herpes type 6 virus (HHV 6)
Lymphocytic choriomeningitis virus (LCMV)	Human Immunodeficiency virus (HIV)
Mumps virus	Jamestown canyon virus
	John Cunningham virus (JC)
	La Crosse virus
	Powassan virus
	St. Louis encephalitis virus
	West Nile virus
	Varicella-zoster virus (VZV)
	Zika virus

Data from references: [3,15–19,35–37,40], and, [42–45].
[a] Account for 99% of cases.
[b] Account for 1% of cases.

Table 3
Etiology of viral meningitis as reported in selected clinical case series.

Author(s)	[Ref]	Years	Cases (n)	ARBO (%)	HSV (%)	LCMV (%)	Mumps (%)	NPEV (%)	P (%)
Adair, et al	3	1947–52	480	NR	5.3	9.7	13.3	NR	NR
Meyer, et al	15	1953–58	430	0.7	1.4	8.8	15.8	29.8	8.8
Buescher, et al	17	1958–63	375	0.8	0.5	1.9	7.5	38.5	4.8
Berlin, et al	18	1986–90	274	NR	NR	NR	NR	61.3	0.007
Kupila, et al	16	1999–2003	144	NR	18.0	NR	NR	23.0	NR
Han, et al	19	2008–2013	177	NR	0.01	NR	0.005	38.4	NR

Abbreviations: ARBO, arboviruses; HSV, herpes simplex virus; LCMV, lymphocytic choriomeningitis virus; NPEV, non-polio enteroviruses; and P, polio virus. NR, not reported.

Viruses are either inhaled (e.g. Mumps) or ingested (non-polio Enteroviruses) to establish primary infection in the oropharyngeal or gastrointestinal lymphoid tissues. Viruses can also establish primary infection of local lymphoid tissues following the skin bite of a mosquito.

↓

Infecting viral pathogens gain entry to the central nervous system (CNS) by directly infecting cerebral vascular endothelial cells, infecting hematopoietic cells that cross the blood brain barrier (BBB), or migration through peripheral sensory or motor neurons. Viruses may also target cells of the meninges or ventricular lining as well as the choroid plexus (e.g. Mumps).

↓

Once viral tropism allows passage to the CNS, infection is characterized by release of chemoattractants in the meninges followed by an ensuing innate immune cell infiltration of neutrophils, monocytes and antiviral CD8 lymphocytes.

↓

Infection of leptomeningeal cells results in viral meningitis with symptoms of fever, headache and stiff neck.

Fig. 1. Pathogenesis of viral meningitis.

Table 6
Clinical manifestations.

Symptoms	NPEV (%)	HSV (%)	LCMV (%)	Mumps (%)
Fever[a]	65–83	6–52	89-98	54–98
Headache[a]	97–100	96–100	98–100	26–97
Neck stiffness[a]	55–69	22–71	67-91	8–85
Arthralgia/myalgia	88	50	56–67	14–21
Nausea/vomiting	50–76	33–83	65–100	18–66
Photophobia	79–85	33–64	19	7

Abbreviations: NPEV, non-polio human enteroviruses; HSV, herpes simplex virus; LCMV, lymphocytic choriomeningitis virus.
Data from references: [3,14,32,35–37,54–56,58,59].
[a] Meningitis is typically characterized by the triad of fever, headache and neck stiffness (e.g. nuchal rigidity).

has been reported in older case series [3].

4.3. Mumps

The most frequent manifestations of mumps meningitis include pain in the area of the parotid glands (91%), swelling of one (47%) or both (46%) parotid glands, fever (54–98%), and headache (26–97%) [3,32,51]. The onset of meningitis occurs on average 2–10 days after the appearance of parotid gland symptoms and signs in the majority of cases [3,32,51]. Other clinical manifestations may include nausea and vomiting (18–66%), swollen and painful testis (15%), arthralgias and myalgias (14–21%), and neck stiffness (8–85%) [3,32]. While fever lasts from 3 to 7 days, devervescence is usually associated with clinical recovery and total duration of illness ranging from 7 to 10 days [3,32,57].

4.4. Herpes viruses

Meningitis associated with Herpesviruses, particularly HSV-2, is usually characterized by severe frontal headache (96–100%), posterior neck stiffness (22–71%), nausea (33–83%), vomiting (33–56%), fever above 38.5 °C (6–52%), photophobia (33–64%), and phonophobia (16%) [3,58,59]. A prior genital herpes infection history has been reported in approximately 9–23% of cases [58,59]. Patients with RBLM characteristically develop multiple meningitis episodes ranging from 2 to 13 episodes per patient with the time between the first and second episode ranging from 10 months to 10 years between episodes and lasting anywhere from 2 to 5 days in duration followed by spontaneous resolution [58,59]. Additional symptoms may include neuropathic pain to the extremities following a specific dermatomal pattern, paresthesias, hallucinations, arthralgias, and difficulties with micturition both during and days to years after the meningitis episode [3,39,58,59]. Varicella zoster virus (VZV) meningitis is characterized most commonly by headache, fever, and stiff neck followed by the onset of herpes zoster (e.g. Shingles); however, cases have been reported to occur without the rash (e.g. zoster sine herpete) [19,60].

Clinical manifestations of viral meningitis other than those caused by the above mentioned are beyond the scope of this review. Selected important emerging arthropod-borne causes of viral meningitis are worth brief review (Table 7). Neuroinvasive manifestations of disease among these pathogens is uncommon.

5. Diagnosis

The sign's of Kernig and Brudzinski, as well as nuchal rigidity, are bedside diagnostic tests used specifically to assess patients with "*suspected meningitis*" (e.g. fever, headache, neck stiffness, photophobia, nausea and vomiting) (Box 2) [61–64]. Russian physician Vladimir Mikhailovich Kernig (1840–1917) published in 1882 his observations that many patients suffering from meningitis demonstrated restriction of passive extension at the knee as the result of hamstring muscle spasm [61]. Although Polish pediatrician, Josef Brudzinski (1874–1917), in his original 1909 article described four clinical maneuvers for the diagnosis of meningitis, the most common maneuver is passive neck flexion resulting in reflexive flexion of the patient's hips and knees (e.g. nape-of-the-neck sign) [62]. A recent prospective study, by Thomas and colleagues analyzing 297 adults with suspected meningitis, reported a sensitivity of 5% and specificity of 95% for both Kernig's and Brudzinski's signs [63]. Causative pathogens in this cohort included Enteroviruses (8 patients) and VZV (1 patient) [63]. Of the 80 patients with meningitis, 24 had nuchal rigidity (sensitivity, 30%; specificity, 68%) [63]. In a study by Amarilyo and colleagues among 108 children (2 months to 16 years age group) with suspected meningitis (6 bacterial and 52 aseptic) found that Brudzinski and Kernig signs were present in 51% and 27% of the patients, respectively, but when present had relatively high positive predictive values (81% and 77%, respectively) [64]. The authors also reported on the accuracy of photophobia (sensitivity, 28%; specificity, 88%) and the bulging fontanel sign [64].

Headaches known to arise primarily from inflammation or dilation of pain-sensitive intracranial arteries, veins and adjacent meningeal structures, as in meningitis, are observed to be particularly sensitive to head jolting [65–67]. Exacerbation of a baseline headache with jolting is known as *jolt accentuation of headache* (JAH) and suggests an

Table 7
Selected arthropod-borne viruses presenting as meningitis.

Etiology	Historical clues	Physical clues	Laboratory diagnosis
West Nile Virus (WNV)	Transmitted via the bite from an infected *Culex* mosquito. Transmission may also occur with transplantation of WNV-infected organs, breast feeding or transfusion of blood products.	Symptomatic patients may have a "flu-like" illness with fever, headaches and maculopapular rash involving the trunk and limbs. Neuroinvasive disease may manifest as meningitis, encephalitis and acute polio-like flaccid paralysis. Additional neurologic symptoms may include tremors, parkinsonism and myoclonus.	CSF PCR is helpful in early illness prior to antibody production. CSF WNV-specific IgM is also a common laboratory method of diagnosis.
Dengue Virus (DENV)	Endemic throughout the tropics and subtropics (e.g. predominantly Africa, Southeast Asia, Latin America and the Caribbean). Transmitted via the bite from an infected *Aedes* mosquito.	Clinical manifestations are characterized by sudden onset of fever, headache, retro-orbital pain, arthralgia and myalgia, and petechial rash.	DENV-specific PCR or IgM in CSF.
Chikungunya Virus	Endemic mostly during the rainy season throughout the tropics and subtropics (e.g. predominantly Africa, Pacific Islands, Latin America and the Caribbean). Transmitted via the bite from an infected *Aedes* mosquito.	Clinical manifestations are characterized by sudden onset of fever, headache, severe bilateral symmetric joint pains of hands and feet as well as maculopapular rash and conjunctivitis.	Virus specific PCR or IgM in CSF.
Zika virus	Sporadic epidemics throughout the tropics and subtropics (e.g. predominantly Africa, Southeast Asia, Pacific Islands, Latin America and the Caribbean). Transmitted via the bite from an infected *Aedes* mosquito.	Clinical manifestations are characterized by sudden onset of headache, arthralgia and myalgia, and petechial rash, maculopapular rash and conjunctivitis.	Virus specific PCR or IgM in CSF.

Reference(s): Waterman SH, et al. Am J Trop Med Hyg. 2015 May; 92(5):996–8 and Sánchez-Seco MP, et al. Enferm Infecc Microbiol Clin. 2005 Nov;23(9):560–8

intracranial etiology [65–67]. The most common bedside maneuver for a positive test is horizontal rotation of the neck at a rate of 2–3 times per second [65–67]. Three recent prospective studies, analyzing 421 adults with fever, headache and suspected meningitis, reported sensitivities of 6% to 97% and specificities of 60% to 98% in predicting CSF pleocytosis [65–67]. Based on current data the above classic meningeal signs are of limited clinical diagnostic value.

The diagnosis of viral meningitis rests on examination of CSF pleocytosis by lumbar puncture, defined as a white blood cell (WBC) count > 5 cells/mm^3 [11,12,55]. In selected case series the total nucleated WBC count is usually 9 to 2590 cells/mm^3 with a lymphocyte predominance ranging from 24% to 100% (Table 8) [16,19,35,51,54–57,59,68]. Polymorphonuclear leukocytes (PMN) sometimes predominate among early CSF profiles; however, this phenomenon shifts toward a mononuclear predominance (e.g. Lymphocytes) within 18–48 h after the initial examination [69]. While protein concentrations are usually elevated in the range of 40 to 3704 mg/dL, glucose values may be low to normal ranging from 32 to 80 mg/dL [16,19,35,51,54–57,59,68]. CSF lactate concentrations originate from normal anaerobic metabolism and may be elevated by glycolysis in the setting of bacterial meningitis; however, values remain normal with viral meningitis [70]. In one recent prospective study of 176 patients, 51 with bacterial meningitis and 125 with aseptic meningitis/encephalitis, with acute meningitis in which CSF lactate concentrations were > 3.5 mmol/L testing demonstrated diagnostic value to differentiate bacterial from nonbacterial meningitis among persons who had not received prior antimicrobial therapy (sensitivity of 96%; specificity 85%) [70].

Virologic diagnosis historically depended upon detection of complement-fixing and neutralizing antibodies or isolation from CSF in various tissue cultures such as primary rhesus monkey kidney (RMK), neonatal kidney, human embryo lung (MRC-5), and rhabdomyosarcoma cells within 24 h of sample collection [3,14,16,55,56,71]. No single cell line is optimal for culture and the mean time for cytopathogenic effect (CPE) can range from 2 to 14 days from CSF samples and 5 to 14 days for both stool and throat swab specimens [55,71]. The value of positive culture CPE from various sites include 6% to 91% for CSF, 19% to 78% for stool, and 5% to 77% for throat samples, indicating culture results are insensitive for the diagnosis of viral meningitis [16,55,71]. Additionally, the average time of appearance for complement-fixing and neutralizing antibodies to diagnostic levels usually occurs 3–4 weeks after the onset of illness [3]. Since conventional means of diagnosis is time consuming and lacks sensitivity, nucleic acid sequence-based amplification tests (NAAT), such as polymerase chain reaction (PCR), have revolutionized detection of viral pathogens and have emerged as the new gold standard (Table 9) [14,16,19,54–56,71–76]. The technical complexity of most NAATs requires that they are run in batches and restricts their availability to high-complexity laboratories with appropriate expertise in molecular diagnostics. Various assays have been used for the detection of NPEV by employing reverse-transcription PCR (RT-PCR) with primers targeting the conserved 5′ noncoding region of complementary deoxyribonucleic acid (cDNA), particularly VP1 [71–76]. Described methods include real-time and conventional RT-PCR, including single RT-PCR, nested RT-PCR, and multiplex RT-PCR (Table 10). It is important to note that these assays are all laboratory-developed methods that vary greatly in complexity, performance characteristics, and time to completion. The first NAAT cleared by the US Food and Drug Administration (FDA) on March 16, 2017 for the detection of NPEV RNA was the Xpert EV assay (Cepheid, Sunnyvale, CA) [75]. In a multicenter study of 199 evaluable CSF specimens collected between July and December 2005 authors reported the overall performance characteristics of the Xpert EV assay had a sensitivity of 94.69% (90% confidence interval [CI]), specificity of 100% (90% CI), positive predictive value of 100%, and negative predictive value of 98.17% [75]. The authors reported detection of coxsackievirus serotypes A9 and B2-5, Echovirus serotypes 3, 6, 7, 9, 11, 13, 15, 18, 25 and 30, and Enterovirus serotype 71 with this assay within 2.5 h [74,75].

Box 2
Classic meningeal signs.

Kernig's sign – With the patient's hips and knees flexed, a positive sign is when the patient resists extension of the knee. The test was originally performed with a patient seated on the edge of the bed and feet dangling over the side.

Brudzinski's sign – Flexion of the supine patient's neck causes the patient to flex both hips and knees; therefore, retracting the legs toward the chest.

Nuchal rigidity – Neck stiffness denoting involuntary resistance to passive neck flexion.

Table 8
Viral meningitis CSF pleocytosis among selected case series.

	Normal CSF	NPEV	HSV/VZV	LCMV	Mumps
WBC (cells/mm^3)	< 5 cells/mm^3	9–2590 cells/mm^3	46–1860 cells/mm^3	415–1715 cells/mm^3	77–1600 cells/mm^3
Lymphocytes (%)	0–30%	24–100%	80–100%	95–100%	77–100%
Glucose (mg/dL)	45–80 mg/dL	[a]45–80 mg/dL	32–80 mg/dL	43–68 mg/dL	NR[b]
Protein (mg/dL)	15–45 mg/dL	277–1540 mg/dL	404–3215 mg/dL	128–240 mg/dL	40–74 mg/dL

Abbreviations: NPEV, non-polio human enteroviruses; HSV, herpes simplex virus; LCMV, lymphocytic choriomeningitis virus.
Data from references: [6,19,35,51,54–57,59,65].
[a] Some values were originally reported as mmol/L. To convert mmol/L to mg/dL, multiply by 18. To convert mg/dL to mmol/L, divide by 18.
[b] NR = Not reported.

Table 9
Diagnostic evaluation to consider in patients with viral meningitis.
Adapted from Tunkel AR, et al. Clin Infect Dis. 2008 Aug 1;47(3):303–27.

Microbial cause	Key diagnostic test
Non-polio Enteroviruses (NPEV)	CSF PCR
Epstein-Barr virus (EBV)	Serology for VCA IgM and IgG, EBVNA IgG, and CSF PCR
Herpes simplex virus (HSV)	CSF PCR
Human immunodeficiency virus (HIV)[a]	Serology
Mumps	Serology
Varicella zoster virus (VZV)	CSF PCR

Abbreviations: PCR = polymerase chain reaction, VCA = viral capsid antigen, EBVNA = Epstein-Barr virus nuclear antigen.
[a] In patients who are HIV seronegative but there remains a high index of suspicion for infection, plasma HIV RNA testing should be performed.

6. Management

Antiviral chemotherapy directed against NPEV is not FDA approved or routinely available and management is mainly supportive (Box 3). Guidelines from the Infectious Disease Society of America (IDSA) regarding the management of encephalitis recommend adjunctive corticosteroids for selected viral pathogens (e.g. VZV, EBV) may be considered; however, there are no reliable controlled trial data to support their routine use with these recommendations being based primarily on clinical experience, descriptive studies, or reports of expert committees [C-III evidence rating] [76]. Although controlled trial data supports the use adjunctive corticosteroids for bacterial meningitis (e.g. *Streptococcus pneumonia* or *Mycobacterium tuberculosis*), therapy administration for viral meningitis is not currently recommended [76–79].

Pleconaril is a novel, orally bioavailable, and systemically acting small-molecule inhibitor of enteroviruses and rhinoviruses that inhibits replication by integration with the viral capsid preventing cell to cell attachment and uncoating of viral RNA [80]. Among picornavirus-infected patients enrolled in placebo-controlled trials, no significant differences in duration of positivity by culture or PCR, hospitalization or symptoms were detected between groups [81,82]. Additionally, adverse events such as nausea and diarrhea were more common in the treatment groups as well as potential drug-drug interaction due to induction of cytochrome P-450 3A enzymes [82].

Although HSV type-1 typically causes encephalitis and HSV type-2 meningitis, both virus types have been reported to cause either encephalitis or meningitis [83]. While guidelines from the Infectious Disease Society of America (IDSA) regarding the management of HSV encephalitis recommend initiation of intravenous acyclovir at 10 mg/kg every 8 h in reducing morbidity and mortality, there are no current guidelines or controlled clinical trials to guide the optimal treatment of HSV meningitis among immunocompetent patients [76,83]. Based upon limited retrospective data, symptomatic treatment alone has been suggested for immunocompetent patients as HSV-associated meningitis typically improves with or without specific antiviral therapy [68,83,84]. Noska and colleagues evaluated the benefit of antiviral therapy without adjuvant corticosteroids in a retrospective observational study among forty-two immunocompromised patient episodes of HSV meningitis and reported fewer neurologic sequelae with a 7 to 10-day course of therapy [83]. Authors also reported no neurologic sequelae were noted among immunocompetent patients [83]. Although one single non-randomized retrospective study of 45 patients with HSV encephalitis (HSVE) indicates the superiority of a combination of acyclovir plus prednisone, this finding has not been demonstrated among patients with HSV meningitis [85]. A prospective, randomized, double-blind, placebo- controlled multicenter trial among 101 patients with HSV-2 meningitis demonstrated no benefit in preventing recurrences with suppressive therapy using twice daily valacyclovir [84].

7. Conclusion

Aseptic meningitis has been recognized since the introduction of lumbar puncture in the early 20th Century. Although notions of infecting viral pathogens were novel to the intellectual course in early investigations of viral meningitis constructed by Wallgren, understanding the pathogenesis of disease has evolved in staccato fashion over several decades, culminating now with reliable diagnostic and medical treatment methods. Although NPEV are the most common viral pathogens, other agents should be considered in the differential diagnosis. Molecular diagnostic methods have emerged as the gold standard for diagnosis and should be used when considering antiviral therapy. Most cases are adequately treated with supportive therapy alone; however, a small subset of patients may benefit from short courses of antiviral treatment for selected pathogens and medical conditions.

Table 10
Diagnostic performance of nucleic acid amplification methods.

Virus	Sensitivity	Specificity	Reference(s)
NPEV	95%	100%	Marlowe EM, Novak SM, Dunn JJ, et al. Performance of the GeneXpert enterovirus assay for detection of enteroviral RNA in cerebrospinal fluid. J Clin Virol. 2008 Sep; 43(1):110–3
HSV-1	100%	98.7%	Shi X, Wu R, Shi M, et al. Simultaneous detection of 13 viruses involved in meningoencephalitis using a newly developed multiplex PCR Mag-array system. Int J Infect Dis. 2016 Aug; 49:80–6; Lévêque N, Legoff J, Mengelle C, et al. Virological diagnosis of central nervous system infections by use of PCR coupled with mass spectrometry analysis of cerebrospinal fluid samples. J Clin Microbiol. 2014 Jan; 52(1):212–7; and Bøving MK, Pedersen LN, Møller JK. Eight-plex PCR and liquid-array detection of bacterial and viral pathogens in cerebrospinal fluid from patients with suspected meningitis. J Clin Microbiol. 2009 Apr; 47(4):908–13.
HSV-2	100%	98.2%	
CMV	100%	99.4%	
VZV	94–100%	99.4%	
EBV	31–100%	97–99.4%	

Abbreviations: NPEV, non-polio human enteroviruses; HSV, herpes simplex virus; CMV, cytomegalovirus; VZV, varicella-zoster virus; and EBV, Epstein-Barr virus.

Box 3
Treatment of viral meningitis.

Non-polio Enterovirus infections (NPEV) – Supportive therapy as pleconaril is not FDA approved and has no demonstration of efficacy.

Herpes simplex (HSV) and varicella zoster virus (VZV) – Supportive therapy in association with short courses (7–10 days) of acyclovir at 10 mg/kg intravenously every 8-h or valacyclovir 1 g oral every 8-h. There is no efficacy for antiviral suppression therapy.

Human immunodeficiency virus (HIV) – Supportive therapy in association with infectious diseases consultation for early initiation of highly active antiretroviral therapy (HAART).

Mumps – Supportive therapy in association with adherence to the recommended immunization schedules by the Advisory Committee on Immunization Practices (ACIP).

While this review covered the most common viral causes of meningitis, it is not exhaustive, and considerations should be made for unusual pathogens that may vary based on patient exposures (e.g. location, travel, hobbies); a collaborative effort between neurology and infectious disease is often warranted in these situations.

Declarations of interest

We declare no competing interests.

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None.

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