Acute Aseptic Meningitis Syndrome

4

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Wallgren initially described the aseptic meningitis syndrome in 1925 as an acute community-acquired syndrome with cerebrospinal fluid (CSF) pleocytosis in the absence of a positive Gram stain and culture, without a parameningeal focus or a systemic illness and with a good clinical outcome [1]. It was not until the 1950s when advances in diagnostic virology identified seasonal patterns and a major role for viruses. Since then this clinical syndrome has been used more broadly and includes more than 100 infectious and noninfectious etiologies with some of them being treatable (see Table 4.1). The most common etiologies of aseptic meningitis in the United States (USA) are viruses such as *Enterovirus*, herpes simplex type 2, and West Nile virus although up to 81% of adults remain with unknown etiologies, especially when PCR testing is not routinely done [2]. Acute meningitis is defined as duration of symptoms of less than 5 days and accounts for 75% of all community-acquired meningitis cases [3]. In this chapter, we will review the diagnostic and management challenges to some of the most common causes of acute aseptic meningitis syndrome. We will briefly discuss herpes viruses, arboviruses, dengue, Zika, chikungunya, syphilis, partially treated bacterial meningitis, human immunodeficiency virus, and Lyme disease as other chapters in this book cover these etiologies extensively.

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Table 4.1 Differential diagnosis of acute aseptic meningitis syndrome

Infectious etiologies
Viruses
Enteroviruses[a]; arboviruses[b]; herpes viruses[c]; mumps virus; polio viruses
Lymphocytic choriomeningitis virus; human immunodeficiency virus[d]
Adenovirus; parainfluenza virus; influenza A and B; measles; rubella
Bacteria
Bacterial meningitis; parameningeal focus[e]; *Rickettsia* species; endocarditis
Ehrlichia; *Anaplasma* spp.; *Brucella* species; *Bartonella henselae*;
Nocardia spp.; *Mycoplasma* spp.; *Mycobacterium tuberculosis*
Spirochetes
Treponema pallidum (syphilis); *Borrelia burgdorferi* (Lyme disease); *Leptospira* spp.;
Protozoa and helminths
Naegleria fowleri; Angiostrongylus cantonensis; Baylisascaris procyonis
Taenia solium; Toxocara spp.; *Strongyloides stercoralis* (hyperinfection syndrome)
Noninfectious etiologies
Intracranial tumors and cysts
Craniopharyngioma; teratoma[f]; dermoid/epidermoid cyst
Medications
Antimicrobial agents[g]; nonsteroidal anti-inflammatory agents[h]; muromonab-CD3 (OKT3)
Azathioprine; cytarabine; carbamazepine[h]; immune intravenous globulin; ranitidine
Systemic illnesses
Systemic lupus erythematosus; Behçet's disease; sarcoidosis; Vogt-Koyanagi-Harada
Procedure related
After neurosurgery ("chemical meningitis"); spinal anesthesia; intrathecal injections[i]
Miscellaneous
Seizures; migraine or migraine-like syndromes; postvaccination; meningeal carcinomatosis
Multiple sclerosis; heavy metal (lead and mercury) poisoning; vein of Galen aneurysm

[a]Primarily echoviruses and coxsackieviruses

[b]In the USA, the major etiologic agents are the mosquito-borne West Nile virus, California, St. Louis, and Eastern equine encephalitis and the tick-borne Colorado tick fever

[c]Primarily herpes simplex virus type 2 but also herpes simplex virus type 1, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, and human herpesvirus 6

[d]During the acute HIV seroconversion syndrome

[e]Brain abscess, sinusitis, otitis, mastoiditis, subdural empyema, epidural abscess, venous sinus thrombophlebitis, pituitary abscess, cranial osteomyelitis

[f]Main association of the anti-NMDA receptor encephalitis in young women

[g]Trimethoprim, sulfamethoxazole, trimethoprim-sulfamethoxazole, ciprofloxacin, penicillin, isoniazid, metronidazole, cephalosporins, pyrazinamid, Ibuprofen, sulindac, naproxen, tolmetin, diclofenac, ketoprofene

[h]In patients with connective tissue diseases

[i]Air, isotopes, antimicrobial agents, antineoplastic agents, corticosteroids, radiographic contrast media

Infectious Causes

Viral Meningitis

Enteroviruses

Enteroviruses (EV) are the leading recognizable cause of aseptic meningitis syndrome [1, 2]. As the surveillance of EV infections to the Centers for Disease Control and Prevention (CDC) is passive [4] and because enteroviral infections are underdiagnosed as only 15% of adults with aseptic meningitis get a CSF EV polymerase chain reaction (PCR) done [2], the true prevalence of this infection is unknown. A total of 118 types of enteroviruses and 16 types of human parechoviruses (HPeV) have been described as causes of viral meningitis in the USA [4, 5]. EV can sometimes also cause acute flaccid paralysis, encephalitis, myocarditis, and sepsis with worse clinical presentations most commonly seen in neonates or infants [5, 6]. Enterovirus D68 has been implicated as a possible cause of acute flaccid paralysis (AFP) in the USA as 43% of cases have had the virus isolated from respiratory specimens by PCR [6]. Enteroviruses have a worldwide distribution, and in temperate climates they have a summer/fall seasonality [1, 2, 5]. Transmission is via the fecal-oral route and less likely by respiratory droplets [5]. A report from the National Enterovirus Surveillance System from the CDC from 2009 to 2013 documented the seasonal pattern (April to November) with the two most common viruses identified as coxsackievirus A6 and human parechovirus type 3 [4].

Infants and young children most commonly suffer from enteroviral meningitis because they are the most susceptible host population within the community. Risk factors for severe disease in children are absence of oral lesions, seizures, and lethargy [7]. In adults, enteroviruses more commonly present with aseptic meningitis with good clinical outcomes [2]. Rarely, patients can present with an enteroviral meningoencephalitis after receiving chimeric anti-CD20 monoclonal antibody rituximab [8]. Additionally, neonates can present with a severe form of meningoencephalitis with symptoms and signs developing at birth after transplacental transmission of the virus. With disease progression, a sepsis-like syndrome characterized by multiorgan involvement, disseminated intravascular coagulation, seizures, focal neurological signs, and cardiovascular collapse may develop [5]. A recent small clinical trial showed that pleconaril improved clearance of the virus and mortality in neonates with enteroviral sepsis, but the Federal Drug Administration (FDA) [9] has not approved the drug.

Severe disease and poor outcome are rare in infants, children, and adults [2, 10]. Infants usually present with fever, irritability, feeding difficulties, and rash with the majority of them having a good clinical outcome [5, 10]. Approximately one-third of patients have stiff neck with less than 2% of patients presenting with altered mental status. Headache is nearly always present in adults, but photophobia is seen in ~ one-third of patients [11]. Patients may also present with nonspecific symptoms and signs such as vomiting, anorexia, rash, diarrhea, cough, upper respiratory tract findings, and myalgias. The duration of illness in enteroviral meningitis is usually

less than 1 week, with many patients reporting improvement after lumbar puncture, presumably from reduction in intracranial pressure [1, 5].

Herpes Viruses

Herpes viruses include herpes simplex virus (HSV) types 1 and 2, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, and human herpes viruses 6, 7, and 8 [1]. Although neurologic complications are known to occur with some of these viruses, complications associated with HSV are of the most significance. In a recent study of 404 adults with aseptic meningitis, HSV was the most common identified viral pathogen even though only 39% of patients had a CSF HSV PCR performed [2]. In patients beyond the neonatal period, it is critical to differentiate between HSV encephalitis (usually HSV type 1), a potentially fatal infection, and HSV meningitis (most commonly by HSV type 2), a self-limited syndrome. The syndrome of HSV-2 aseptic meningitis is most commonly associated with primary genital infection and has a benign clinical outcome that does not appear to be impacted by antiviral therapy [12]. HSV-2 is also the most common cause Mollaret's meningitis (now termed *recurrent benign lymphocytic meningitis*), although a few cases have been associated with HSV-1 and Epstein-Barr virus have been reported [13]. The majority of patients are female, have no history of genital HSV and have no active lesions on presentation [13]. A recent double blind, randomized clinical trial of valacyclovir suppression showed no impact on decreasing recurrent rates in patients with HSV-2 meningitis [14]. Acute aseptic meningitis has also been associated with varicella-zoster virus (VZV) in patients with or without typical skin lesions, [12] the latter known as *zoster sine herpete.* VZV is most likely an underdiagnosed treatable etiology as only 1.2% of patients with aseptic meningitis undergo a CSF VZV PCR [2]. A recent study using a multiplex PCR documented that human herpes virus 6 (HHV-6) was more commonly detected than HSV-1 or HSV-2 in adults and children with meningitis and encephalitis [15]. The proportion that these HHV-6 cases represent a true infection versus reactivation or chromosomal integration remains to be determined [16]. Cytomegalovirus and Epstein-Barr virus may cause aseptic meningitis in association with a mononucleosis syndrome, particularly in an immunocompetent host [1].

Arboviruses

Arboviruses (arthropod-borne virus) include several families of viruses that are transmitted by either mosquitos, ticks, or sandflies [17]. The most common arthropod-transmitted cause of aseptic meningitis in the USA is West Nile virus (WNV), a flavivirus. WNV infection is most commonly asymptomatic with approximately 20% having a febrile illness and 1% presenting with neuroinvasive disease [18]. Neuroinvasive disease may present with an aseptic meningitis, with encephalitis, or with an acute flaccid paralysis/myelitis but may be underdiagnosed as only approximately one-third of adults and children with meningitis or encephalitis get tested [19]. There is no vaccine or therapy for WNV.

Neuroinvasive disease develops in approximately 1% of patients with West Nile virus infections during the summer months in the USA [19]. Patients can present with meningitis, encephalitis, or acute flaccid paralysis with up to 50% of patients with

encephalitis having concomitant chorioretinitis [20]. Patients with meningitis typically presents with fever, headache, nausea, vomiting, stiff neck, photophobia, and occasionally with a maculopapular rash [17]. In addition, patients may have persistent headaches, memory impairment, and chronic fatigue years after infection [21].

Other less common arboviruses in the USA that can cause aseptic meningitis are the two mosquito-borne illnesses, St. Louis encephalitis (a flavivirus) and the California encephalitis group of viruses (e.g., La Crosse, Jamestown Canyon, and snowshoe hare viruses, which are bunyaviruses), and two tick-borne illnesses, Powassan virus in northern central and eastern USA and coltivirus (agent of Colorado tick fever) in the mountainous and western regions of the USA and Canada [17]. In 2015, the CDC reported a total incidence of 2175 cases of WNV followed by La Crosse (55), St. Louis (23), Jamestown canyon (11), Powassan (7), and Eastern equine encephalitis (6) [22]. In Europe, tick-borne encephalitis can be associated with a complex syndrome of meningoencephaloradiculitis (MER), which is associated with a relatively high risk of severe disease (requirement for intensive care and mechanical ventilation). Age, male sex, and preexisting diabetes mellitus were predictive of the more severe MER [23]. Toscana virus has emerged as one of the most common causes of meningitis or encephalitis during the summer in the Mediterranean countries [11]. It is transmitted by sandflies and is caused by a bunyavirus.

Other Viruses

Lymphocytic choriomeningitis virus (LCMV) can cause aseptic meningitis; this virus is now rarely reported as an etiologic agent [1]. A seroprevalence of 5% for LCMV was seen in 400 patients with neurological infections in Finland [24]. LCMV is transmitted to humans by contact with rodents (e.g., hamsters, rats, mice) or their excreta [1, 24]; the greatest risk for infection is in laboratory workers, pet owners, and persons living in impoverished and unhygienic situations. Recent outbreaks have been reported in rodent breeding factories or infected households [25, 26]. No evidence of human-to-human transmission has been reported.

In an unimmunized population, mumps can cause aseptic meningitis [1]. With the introduction of the measles-mumps-rubella (MMR) vaccine, the incidence of mump-associated meningitis has dramatically decreased with now only accounting for <1% of all cases of meningitis and encephalitis in the UK and US [27, 28].

Human immunodeficiency virus (HIV) can cause aseptic meningitis during HIV seroconversion presenting clinically with a mononucleosis-like picture [1]. HIV may also cause an encephalitis presentation in those with acquired immunodeficiency syndrome (AIDS) who are not receiving antiretroviral therapy (ART) (known as AIDS encephalopathy or HIV encephalitis) or in those patients on ART with CSF viral escape (detectable viral load in the CSF with undetectable or low-level viremia) [29]. This latter form is referred to as CD8 encephalitis and can be treated with steroids and by optimizing ART.

Japanese encephalitis is a vaccine preventable infection that continues to cause both meningitis and encephalitis in countries where routine vaccination is not available [30]. Dengue, chikungunya, and Zika virus are emerging causes of meningitis

or encephalitis in several parts of the world [31, 32]. The epidemic of Ebola disease in West Africa has revealed unusual characteristics of the disease not previously described, including viral relapse with acute meningitis, with high levels of virus in the cerebrospinal fluid. Antiviral therapy with an experimental agent and adjuvant corticosteroids led to resolution of the disease [33].

Bacterial Etiologies

Patients with bacterial meningitis may present with a negative Gram stain [34]. Patients with bacterial meningitis classically present with fever, headache, meningismus, and signs of cerebral dysfunction; however, clinical presentation may vary based on age and underlying disease status and as a result of infection by specific bacterial pathogens. Even though the CSF typically shows a >1000 WBC per mm^3 with a neutrophilic predominance, a CSF protein >100 mg/dl and a glucose <40 mg/dl, a neutrophilic pleocytosis, and hypoglycorrhachia may be seen in viral meningitis as well [35, 36]. Patients with infective endocarditis due to *Staphylococcus aureus* and *Streptococcus pneumoniae* can sometimes present with meningitis [1]. Additionally, patients with parameningeal focus of infections may sometimes present with meningitis. Epidural or subdural empyemas may sometimes occur to contiguous osteomyelitis complicating sinusitis, otitis, or mastoiditis [1].

Spirochetal Meningitis

Treponema pallidum disseminates to the CNS during early infection [37]. The organism can be isolated from the CSF of patients with primary syphilis, and CSF laboratory abnormalities are detected in 5–9% of patients with seronegative primary syphilis. The actual rate of invasion of the CNS during these early stages is likely to be considerably higher, however. Clinical neurosyphilis can be divided into four distinct syndromes [37]: syphilitic meningitis, meningovascular syphilis, parenchymatous neurosyphilis, and gummatous neurosyphilis.

Lyme disease, most commonly caused by *Borrelia burgdorferi*, can cause an aseptic meningitis in the secondary phase typically 2–10 weeks after the erythema migrans rash [38]. Because viral meningitis is an important differential diagnosis, a clinical prediction rule has been used to help clinicians differentiate these two conditions. The "Rule of 7's" classifies children at low risk for Lyme meningitis when each of the following 3 criteria are met: <7 days of headache, <70% cerebrospinal fluid (CSF) mononuclear cells, and absence of seventh or other cranial nerve palsy [39]. The best currently available laboratory test for the diagnosis of Lyme disease is demonstration of specific serum antibody to *B. burgdorferi,* and this positive test in a patient with a compatible neurologic abnormality is strong evidence for the diagnosis [38].

Leptospirosis can cause aseptic meningitis during the second (immune) phase of the illness and is typically associated with uveitis, rash, conjunctival suffusion,

adenopathy, and hepatosplenomegaly [40]. The CSF profile resembles viral meningitis with the diagnosis being established by CSF or urine culture using Fletcher's medium or by serology. The treatment is doxycycline.

Protozoal and Helminthic Meningitis

Amebas

Despite the hundreds of species of free-living amebas that are known, only a few have been reported to infect humans [41]. The most important are in the genera *Naegleria, Acanthamoeba,* and *Balamuthia. Naegleria fowleri,* the main protozoan causing primary amebic meningoencephalitis in humans, has been recovered from lakes, puddles, pools, ponds, rivers, sewage sludge, tap water, air conditioner drains, and soil [41, 42]. Sporadic cases of primary amebic meningoencephalitis occur when persons, usually children and young adults, swim or play in water containing the amebas or when swimming pools or water supplies have become contaminated, often through failure of chlorination. In the largest review of 142 cases reported in the USA from 1937 to 2013, cases were reported in most southern states and occurred primarily in previously healthy young males exposed to warm recreational waters, especially lakes and ponds, in warm weather locations during summer months [42]. Clinical presentation and CSF formula resembles bacterial meningitis with a mortality of 98%. Recently, miltefosine has resulted in survival in a few cases with *Naegleria fowleri* and *Acanthamoeba* [43, 44].

Eosinophilic Meningitis

Infection of humans by larvae of the nematode *Angiostrongylus cantonensis* is the most common cause of eosinophilic meningitis [45]. Humans become infected by eating infected intermediate hosts (i.e., mollusks, such as snails and slugs) or paratenic (i.e., freshwater prawns, crabs, frogs, and planaria) hosts or by eating food such as leafy green vegetables contaminated by these hosts. The larvae invade the brain either directly from the bloodstream or after migrating through other organs before reaching the spinal cord and brain. Once in the CNS, the larvae mature into adult worms that migrate through the brain. *A. cantonensis* is widespread, and human infection is fairly common and reported from many parts of the world. Other infectious causes of eosinophilic meningitis include *Gnathostoma* species, *Baylisascaris procyonis, Toxocara* species, and *Taenia solium* [45].

Diagnosis

The empirical management of patients is challenging as approximately 93% of patients with community-acquired meningitis present with a negative Gram stain [3]. Furthermore, as the differential diagnosis is broad and available CSF is limited,

the majority of patients do not undergo comprehensive diagnostic evaluations, and several pathogens go undiagnosed [2, 3, 19]. Rapid multiplex PCR testing of the CSF may offer a solution to this dilemma. The BioFire FilmArray Meningitis/Encephalitis (FA ME) (BioFire Diagnostics, Salt Lake City, UT) is the first FDA-approved multiplex PCR panel which detects six bacteria (*S. pneumoniae*, *N. meningitidis*, *S. agalactiae*, *H. influenzae*, *L. monocytogenes,* and *E. coli* K1), seven viruses (HSV types 1 and 2 [HSV-1 and -2], human herpesvirus 6 [HHV-6], cytomegalovirus [CMV], enterovirus, parechovirus, varicella-zoster virus [VZV]), and two fungi (*Cryptococcus gattii/neoformans*) using 0.2 ml of CSF in 1 h. A strategy that uses the panel in meningitis with a negative Gram stain found an increase of 22.9% in diagnoses rendered, mostly commonly viral pathogens, but also two cases with *S. pneumoniae* and a case of *C. gattii/neoformans*. However, 15.2% (5/33) of FA ME-negative isolates were positive by standard assays (four cases of West Nile virus and a case of *Histoplasma capsulatum*, pathogens not included in the panel) [46]. In a retrospective analysis of CSF from HIV patients with cryptococcosis in Uganda, the test was considered useful in distinguishing culture-positive relapse from culture-negative immune reconstitution syndrome [47]. A multicenter prospective study of 1560 patients tested with the panel showed a high sensitivity and specificity for the 14 pathogens in the panel [15]. Other multiplex PCRs that are currently being studied are the Fasttrack, Seegene, and the TaqMan array card assays [48]. Of all these assays, the most comprehensive one is the TaqMan array card that includes 21 pathogens: 2 parasites (*Balamuthia mandrillaris* and *Acanthamoeba*), 6 bacteria (*Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, Mycoplasma pneumoniae, Mycobacterium tuberculosis, and Bartonella*), and 13 viruses (*parechovirus, dengue virus, Nipah virus, varicella-zoster virus, mumps virus, measles virus, lyssavirus, herpes simplex viruses 1 and 2, Epstein-Barr virus, enterovirus, cytomegalovirus, and chikungunya virus*).

Viral Meningitis

Cerebrospinal Fluid Examination

CSF pleocytosis is almost always present in patients with enteroviral meningitis, although some enteroviruses have been isolated from young infants with clinical evidence of meningitis but no CSF white blood cells [5]. A study of 390 patients with enteroviral meningitis showed that 16–18% of children and 68–77% of neonates had no CSF pleocytosis with younger age, lower serum white blood cell count, and shorter duration of symptoms prior to the lumbar puncture being predictors for lack of CSF pleocytosis [49]. The cell count is usually 100–1000/mm^3, although counts in the several thousands have also been reported [5]. Enterovirus can present with a neutrophilic pleocytosis in 39% of patients [35]. If a repeat lumbar puncture is done more than 8 h later, this may switch to a lymphocytic pleocytosis [50], but this practice is done currently in only 0.5% of patients with viral CNS infections [35]. Additionally, a retrospective study of 158 cases of meningitis (138 aseptic and 20 bacterial) showed that 51% of the 53 patients with aseptic meningitis and

duration of symptoms of less than 24 h had a neutrophil predominance in CSF, suggesting that a CSF neutrophil predominance is not useful as a sole criterion in distinguishing between aseptic and bacterial meningitis [51].

Patients with HSV-2 meningitis also present most commonly with a lymphocytic meningitis (<500/mm^3) and a normal glucose content but occasionally can present with a mild hypoglycorrhachia (30–45 mg/dl) or with a neutrophilic pleocytosis [35, 36]. PCR has also become the standard method for diagnosis for all herpes viruses (HSV1, HSV 2, HHSV 6, CMV, EBV, VZV). VZV PCR assay has also confirmed several cases of herpes zoster meningitis even without the typical vesicular rash (zoster sine herpete) [12, 51]. The CSF formula for West Nile virus resembles enteroviral meningitis, and the diagnosis is made by a positive West Nile IgM [19].

Differentiation of Bacterial from Viral Meningitis

Even though the most common causes of meningitis and encephalitis are viral, the majority of patients are admitted and receive empirical antibiotic therapy [28, 34]. In order to aid clinicians, several clinical models have been developed. In one study of 422 immunocompetent patients older than 1 month of age with acute bacterial or viral meningitis, a CSF glucose concentration less than 34 mg/dl, a CSF-to-blood glucose ratio less than 0.23, a CSF protein concentration greater than 220 mg/dl, more than 2000 leukocytes/mm^3 of CSF, and more than 1180 neutrophils/mm^3 of CSF were found to be individual predictors of bacterial rather than viral meningitis, with 99% certainty or better [52]. The Bacterial Meningitis Score has been derived and validated in a total of 4896 patients which identifies children with CSF pleocytosis who were at very low risk for bacterial meningitis (low-risk features were negative CSF Gram stain, CSF absolute neutrophil count <1000 cell/mm^3, CSF protein <80 mg/dl, and peripheral absolute neutrophil count <10,000 cells/mm^3) [53]. Not surprisingly, one of the most important predictors for bacterial meningitis in this scoring system is a positive Gram stain where the diagnosis is not a dilemma to clinicians. A recent study of 960 adults derived and validated a risk score in patients with meningitis and a negative Gram stain that identified a "zero risk" subgroup for any urgent treatable etiology (e.g., bacterial meningitis, herpes simplex encephalitis, fungal encephalitis, etc.) with 100% sensitivity [34]. Even though these clinical models are available, physicians are still treating empirically for bacterial meningitis in the majority of patients [28].

Biomarkers may also aid in the differentiation of viral versus bacterial meningitis. Elevated CSF lactate concentrations may also be useful in differentiating bacterial from nonbacterial meningitis in patients who have not received prior antimicrobial therapy [54, 55]. Two meta-analyses, one including 25 studies with 1692 patients (adults and children) [54] and the other including 31 studies with 1885 patients [55], concluded that the diagnostic accuracy of CSF lactate is better than that of the CSF white blood cell count, glucose concentration, and protein level in the differentiation of bacterial from aseptic meningitis; sensitivities of 93% and 97% and specificities of 96% and 94%, respectively, were seen. C-reactive protein (CRP), detected either

in serum or CSF, and serum procalcitonin concentrations have been elevated in patients with acute bacterial meningitis and may be useful in discriminating between bacterial and viral meningitis. In one study, serum CRP was capable of distinguishing Gram stain-negative bacterial meningitis from viral meningitis on admission with a sensitivity of 96%, a specificity of 93%, and a negative predictive value of 99% [56]. In another study, a serum procalcitonin concentration of more than 0.2 ng/ml had a sensitivity and specificity of up to 100% in the diagnosis of bacterial meningitis, [57] although false-negative results have been reported [58].

Cranial Imaging

Due to the fear of herniation in patients with a possible brain mass, the Infectious Diseases Society of America recommends a head CT before the lumbar puncture with the following criteria: new-onset seizures, an immunocompromised state, signs that are suggestive of space-occupying lesions (papilledema or focal neurologic signs, not including cranial nerve palsy), or moderate to severe impairment of consciousness [59]. Despite these recommendations, the majority of patients with community-acquired meningitis undergo CT scanning with no indications [60]. In a large study of adults and children with aseptic meningitis, all head CT scans that were done were normal [2]. This practice increases costs and delays the diagnosis and therapy of patients with meningitis [61].

Summary of Challenges

- The etiologies of the aseptic meningitis syndrome remain unknown for a large proportion of cases fostering costly admissions, unnecessary antibiotic therapy, and exposure to nosocomial hazards for the majority of patients.
- Utilization of clinical models, biomarkers, and rapid multiplex PCR tests could help identify patients that do not require hospital admission or empiric antibiotic therapy. This could reduce costs and nosocomial complications.
- Cranial imaging is of no diagnostic value in aseptic meningitis and should not be done in patients without indications.

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