Meningitis and Encephalitis

Management and Prevention Challenges

Rodrigo Hasbun
Editor

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Preface

Meningitis and encephalitis continue to be associated with high rates of mortality and neurological sequelae, and despite the availability of molecular diagnostic techniques, the majority of patients have unknown causes. The differential diagnosis is broad and includes a wide spectrum of infectious and noninfectious etiologies, some requiring urgent therapy for survival. Some of the most common challenges clinicians face include the low sensitivity of meningeal signs, overutilization of unnecessary screening cranial imaging in suspected meningitis, delays in the diagnosis of urgent treatable causes, emerging causes of meningitis and encephalitis, large proportion of unknown etiologies, low sensitivity of current microbiological techniques especially in the setting of previous antibiotic therapy, underutilization of available molecular diagnostic tests, and empiric antibiotic therapy and hospitalization for viral meningitis cases. Even though there are published guidelines, compliance with them is not optimal and physicians do not follow standardized algorithms in their empirical approach.

Due to the high rate of adverse clinical outcomes, prevention when feasible is of utmost importance. The use of conjugate vaccines for the three most common meningeal pathogens has dramatically changed the current epidemiology of bacterial meningitis, prenatal screening for Group B streptococcus in pregnancy has decreased early-onset neonatal meningitis, and vaccination for Japanese encephalitis has had a dramatic impact in the countries where it has been implemented. Adherence to protocols to prevent health-care associated meningitis and ventriculitis is effective, but compliance with them is not uniformly performed.

Finally, this book will serve to guide current and future researchers in the field to address the gaps in knowledge that currently exist in the diagnosis, management, and prevention of the most important causes of meningitis and encephalitis in the world with the ultimate goal to improve the outcomes of these devastating clinical syndromes.

Houston, TX, USA — Rodrigo Hasbun

Acknowledgments

This book represents an international collaborative effort to provide the most up-to-date evidence to help diagnose, treat, and prevent the most common central nervous system infections in the world. I want to thank all the experts for providing a thorough and insightful review of the current challenges facing clinicians. I also want to thank the Springer team (Nadina Persaud, Saanthi Shankhararaman, and G. Keerthana) for their excellent support in the organization and production of this book. I would also like to thank the Grant A Starr Foundation for our research support, my research mentor Vinny Quagliarello for the training and support, my wife for her continuous loving support, and for God for guiding my path.

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Introduction

1

Rodrigo Hasbun

Meningitis and encephalitis may be caused by various etiologies, including viruses, bacteria, fungi, protozoa, and helminthes [1, 2]. In addition, numerous noninfectious causes may account for syndromes that mimic central nervous system (CNS) infections [1–3]. These include autoimmune disorders, neoplastic and paraneoplastic diseases, medications, collagen vascular disorders, and other systemic illnesses. CNS infections usually present with cerebrospinal fluid (CSF) pleocytosis and high CSF protein levels due to disruption of the blood brain barrier (BBB) but up to 8% may present without pleocytosis [4]. Despite the availability of microbiological tools, serologies and nucleic acid amplification tests such as single or multiplex polymerase chain reaction (PCR) for the most common infectious agents, the majority of CNS infections currently still remain with an unknown etiology [1, 3, 5]. Meningitis and encephalitis may be associated with significant morbidity and mortality, sometimes requiring emergent neurosurgical interventions or early adjunctive steroids to improve clinical outcomes [1, 3]. Furthermore, CNS infections may also have long-term neurological and neurocognitive sequelae that affect quality of life and activities of daily living. A prompt etiological diagnosis with targeted therapy can improve or prevent several of these adverse clinical outcomes in those with urgent treatable etiologies [1].

Meningitis

Patients with meningitis may have an acute (<5 days duration of symptoms), subacute (6–30 days), or chronic (>30 days) presentation [3], and the clinical manifestations may depend on the virulence of the causative agent and the location of the infection. Patients with acute meningitis usually present with fever, headache, and

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stiff neck seeking medical attention within a few hours to several days after the onset of illness [3]. The presentation may vary, depending on the age of the patient, the causative agent and due to the presence of various underlying conditions (e.g., head trauma, recent neurosurgery, presence of a cerebrospinal fluid [CSF] shunt, and immunocompromised state) [3, 6]. The most common etiologic agents of acute meningitis are unknown [3]. When a cause is identified, the most common etiologies are viruses (most often enteroviruses (children > adults), West Nile virus, and herpes simplex virus type 2 (adults) but also human immunodeficiency virus [HIV], varicella-zoster virus, and less likely mumps virus) and bacteria (e.g., *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Listeria monocytogenes*) [2, 3]. Less commonly, parasites (e.g., *Naegleria fowleri* and *Angiostrongylus cantonensis*) may also cause acute meningitis.

In contrast, patients with subacute or chronic meningitis typically present over weeks to months or even years [3]. These patients are more likely to be immunosuppressed, have abnormal neurological findings, have hypoglycorrhachia, and have a lower CSF pleocytosis [3]. The most common etiology is idiopathic but fungal meningitis (e.g., *Cryptococcus neoformans*, *Histoplasmosis* spp., and *Coccidioides* spp.); *tuberculosis* meningitis, autoimmune disorders, and neurobrucellosis are important causes [3]. Other fungi such as *Candida* spp. in neonates or in patients with ventriculoperitoneal shunts and *Aspergillus* spp. in immunosuppressed individuals are unusual causes of meningitis [2, 3].

Encephalitis

Encephalitis is caused by parenchymal brain inflammation that causes neurological dysfunction [7, 8]. A recent international consortium defined encephalitis with a combination of major and minor criteria [7]. The major criteria is altered mental status lasting >24 h without an alternative diagnosis and is a requirement for the diagnosis. The six minor criteria are (1) documented fever >38 °C (100.4 F) within 72 h before or after presentation, (2) seizures not attributable to a preexisting seizure disorder, (3) new onset focal neurological disorder, (4) CSF WBC > 5/cubic mm, (5) new or acute onset neuroimaging abnormalities consistent with encephalitis, and (6) abnormalities on electroencephalography consistent with encephalitis and not secondary to other etiologies. The presence of 2 minor criteria indicates possible encephalitis, and >3 indicates probable or confirmed encephalitis (if etiological agent is confirmed by brain biopsy, serologies, polymerase chain reaction, or antibodies in autoimmune encephalitis). A clinical overlap between encephalitis and encephalopathy may exist, the latter referring to a clinical state of altered mental status that can manifest as confusion, disorientation, or other cognitive impairment, with or without evidence of brain tissue inflammation; encephalopathy can be triggered by a number of metabolic or toxic conditions but occasionally occurs in response to certain infectious agents such as *Bartonella henselae* and influenza virus [7–9].

Of all the pathogens reported to cause encephalitis, most are viruses that may be associated with specific clinical and neuroimaging findings that suggest their diagnosis [7, 8]. Unilateral temporal lobe encephalitis is classically caused by *herpes simplex virus (HSV)* leading to clinical manifestations characterized by personality changes, altered mentation, a decreasing level of consciousness, seizures, and focal neurologic findings (e.g., dysphasia, weakness, and paresthesias) [7, 8]. Bilateral temporal lobe involvement or lesions outside the temporal lobe, insula, or cingulate are less likely caused by HSV [10]. Other herpes viruses that cause encephalitis during any season include varicella-zoster virus, cytomegalovirus, and human herpes virus 6 and are usually seen more frequently in immunosuppressed individuals. Arboviruses (e.g., West Nile, eastern equine, St. Louis, La Crosse, and Japanese encephalitis viruses) and respiratory viruses can present with thalamic and basal ganglia encephalitis presenting with tremors including Parkinsonism features [11]. Patients with West Nile typically present between June and October, while respiratory viruses usually present in children during the winter season [7, 8]. HIV can present with an encephalitis in AIDS patient without antiretroviral therapy or can present as a CD8 encephalitis in those with immune reconstitution while on antiretroviral therapy [12]. Rabies virus unfortunately is still a frequent cause of encephalitis in Asia (India especially) and in Africa [8]. Enteroviruses are rare causes of encephalitis [7, 8].

Nonviral causes of encephalitis include *Mycobacterium tuberculosis*, *L. monocytogenes*, *Rickettsia*, *Ehrlichia* spp., *Bartonella* spp., *Mycoplasma pneumoniae*, and *Toxoplasma gondii* (more often seen in transplant patients with *Toxoplasma* encephalitis) [7, 8]. Several free-living amebae (i.e., *Naegleria fowleri*, *Acanthamoeba* spp., and *Balamuthia mandrillaris*) may cause a fatal meningoencephalitis during the summer [7, 8]. Other epidemiologic clues that may be helpful in directing the investigation for an etiologic agent in patients with encephalitis include geographic locale, prevalence of disease in the local community, travel history, recreational activities, occupational exposure, insect contact, animal contact, vaccination history, and immune status of the patient [7, 8]. In many cases of encephalitis (32–75%), the etiology remains unknown, however, despite extensive diagnostic testing [7, 8]. In addition, it is important to distinguish between infectious encephalitis and autoimmune encephalitis (antibody mediated or postinfectious or postimmunization) acute disseminated encephalomyelitis (ADEM). These latter syndromes are presumed to be mediated by an immunologic response to an antecedent antigenic stimulus provided by the infecting microorganism or immunization [7, 8]. Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis [13, 14] is the most common cause of antibody-associated encephalitis and is typically seen in young females with an associated ovarian teratoma. Anti-NMDAR encephalitis has now been associated with both herpes simplex virus and varicella-zoster infections [15].

This book reviews the different diagnostic and management challenges that clinicians still face for the most common causes and for some of the emerging etiologies of meningitis and encephalitis in the world. The overall goal of this book is to review the current knowledge and research gaps with hopes to guide future investigators to improve the diagnosis, therapy, and outcomes for CNS infections.

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Community-Acquired Acute Bacterial Meningitis

2

Martin Glimaker

Etiology and Epidemiology

Streptococcus pneumoniae, *Neisseria meningitidis*, and *Haemophilus influenzae* have been the dominating bacteria for many years [1–4]. During the last decades, the incidence of bacterial meningitis has decreased from 2–4/100,000 to 1–2/100,000 in children after implementation of vaccines against *Haemophilus influenza* type B, *Streptococcus pneumonia*, and *Neisseria meningitidis* [3, 5, 6]. *Haemophilus influenzae* has almost disappeared among children, and the number of children with pneumococcal meningitis has also decreased [7]. In adults, where pneumococci is the most common meningeal pathogen, the incidence is relatively stable about 2/100,000 inhabitants. In neonates, up to an age of 4–6 weeks, group B streptococci (*Streptococcus agalactiae*), *Escherichia coli*, other enterobacteriacae, and *Listeria monocytogenes* dominate as etiological agents [8, 9]. *Listeria monocytogenes* may also cause blood stream infection and meningitis in the elderly and/or immunocompromised individuals [10, 11]. Alpha-hemolytic streptococci may be the etiological agent in a few percent of meningitis cases, especially if the infectious focus is present in the sinus, teeth, or heart valve, whereas beta-hemolytic streptococci are more seldom the etiological agent [12]. Patients with *Staphylococcus aureus* endocarditis or spondylodiscitis sometimes also suffer from meningitis [13]. Resistant gram-negative bacteria such as *Pseudomonas aeruginosa*, extended spectrum beta-lactamase (ESBL)-producing bacteria, or *Acinetobacter baumannii* are very seldom found in acute community-acquired bacterial meningitis [4]. The dominating etiologies in different patient categories are summarized in Table 2.1.

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Table 2.1 Dominating etiologies and recommended empiric antibiotic treatment in different patient categories

Patient category	Dominating etiologies	First-line empiric antibiotic treatment	Empiric antibiotic treatment if penicillin allergy	Empiric antibiotic treatment if cephalosporin/meropenem allergy
Infants up to age 4–6 weeks	*S. agalactiae* *E. coli* Enterobacteriacae *L. monocytogenes*	Cefotaxime or ceftriaxone + ampicillin	Meropenem	Meropenem or ampicillin + gentamycin (or other aminoglycoside)
Children older than 4–6 weeks and adults up to age 50 years	*S. pneumoniae* *N. meningitidis* *H. influenzae*	Cefotaxime or ceftriaxone ± vancomycin[a]	Cefotaxime or ceftriaxone[a]	Moxifloxacin + vancomycin or linezolid
Adults over 50 years old	*S. pneumoniae* *N. meningitidis* *H. influenzae* *L. monocytogenes*	Cefotaxime or ceftriaxone + ampicillin ± vancomycin[a]	meropenem[a]	Moxifloxacin + vancomycin or linezolid + trimethoprim-sulfamethoxazole
Immunocompromised patients irrespective of age	*S. pneumoniae* *N. meningitidis* *H. influenzae* *L. monocytogenes*	Cefotaxime or ceftriaxone + ampicillin ± vancomycin[a]	Meropenem[a]	Moxifloxacin + vancomycin or linezolid + trimethoprim-sulfamethoxazole

[a]Vancomycin is added if the incidence of cephalosporin resistant *S. pneumoniae* is >1%

Pathophysiology

Colonization of the upper respiratory tract with *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* is often found in healthy children. The reason why most children do not develop invasive disease whereas a few suffer a fulminant disease with meningitis is not yet well known. Meningitis cases often experience prodromal symptoms from the respiratory tract, such as otitis, sinusitis, pharyngitis, or pneumonia [4]. To cause meningitis the bacteria must break the mucosal barrier of the respiratory tract to invade the blood stream, resulting in a bacteremia, and then the bacteria also have to cross the blood-brain or blood-cerebrospinal fluid barrier [14]. A bacterial spread from a continuous source such as otitis, mastoiditis, or sinusitis may also occur. Once inside the central nervous system (CNS), the bacteria may grow rapidly because of a relative lack of immune system. Impaired mental status, neonatal or high age, comorbidity with immunocompromised state, non-meningococcal etiology, and fulminant disease are reported risk factors for poor outcome.

Acute bacterial meningitis is associated with increased intracranial pressure, which may cause a reduced cerebral blood flow resulting in ischemia or infarction, and also brain herniation [15–21]. The pathophysiological mechanisms resulting in increased intracranial pressure are multifactorial [22, 23]. The release of bacterial components in the subarachnoid space leads to an inflammatory response with a cytokine burst that contributes to (1) increased permeability of the blood-brain barrier causing cerebral extracellular edema, (2) impaired cerebrospinal fluid absorption with increased cerebrospinal fluid volume, (3) a cytotoxic intracellular brain edema, and (4) increased cerebral blood flow (hyperaemia) with microvascular leakage increasing the extracellular edema. All these events are adding to elevated intracranial pressure. Complications to acute bacterial meningitis are vasculitis, ventriculitis, subdural empyema, and brain abscess. The most important systemic complication is septic shock with multiorgan failure and disseminated intravascular coagulation, which may occur especially in meningococcal disease, a condition with very high mortality.

Clinical Picture

Acute bacterial meningitis is a fulminant condition, and the patients may deteriorate rapidly before or shortly after admission. The typical symptoms are fever, headache, neck stiffness, and impaired mental status. Two of these four symptoms are present in 90–95% of cases, whereas all these symptoms occur in only 30–40% [4]. Hence, the clinical picture is atypical in the majority. The patients often suffer from nausea and vomiting, and photophobia and hypersensitivity to sound is common. Positive Kernig's and Brudzinsky's signs may be noticed, but the sensitivity of these signs is low. Prodromal symptoms are often signs of respiratory tract infection, such as

earache, rhinorrhea, and/or cough in pneumococcal meningitis or sore throat in meningococcal disease. In meningococcal cases a petechial rash is often present which may be associated with severe sepsis and septic shock with multiorgan failure. In the elderly the typical symptoms are often more absent making the diagnosis more difficult to set on clinical grounds [10]. Convulsions, as new-onset seizures, occur in about 10–15%, especially in children, and focal neurologic deficit, usually cranial nerve palsy, is observed in about 5% of patients with acute bacterial meningitis. Some patients present with psychomotor anxiety, which can be severe indicating high intracranial pressure and a risk for rapid deterioration into coma and cerebral herniation. Signs of herniation are coma combined with rigid dilated pupils, abnormal breathing pattern, increasing blood pressure combined with bradycardia, opisthotonus, or loss of all reactions.

A characteristic feature in acute bacterial meningitis is the rapid but gradual progression of cerebral symptoms over hours resulting in that the patients usually call on hospital care within 12–24 h [4]. This is in contrast to the clinical picture in patients with cerebral mass lesion, such as brain abscess, where the cerebral symptoms usually develop more slowly over several days and the patients apply hospital care after about a week of cerebral symptoms [24, 25]. The clinical findings are also different in subarachnoid bleeding where severe headache usually appears momentarily in seconds ("thunder headache") and in stroke where neurologic deficit presents suddenly. The most common differential diagnosis is viral meningitis with similar symptoms such as fever, headache, and neck stiffness, but in patients with viral meningitis, the mental status is usually not affected, and the duration of symptoms is usually longer compared to bacterial meningitis [26]. In viral encephalitis, especially herpes simplex encephalitis, the patients initially often present with severe confusion, disorientation, and/or dysphasia but often with relatively normal level of consciousness in contrast to bacterial meningitis where the level of consciousness is often decreased early in the course of disease.

In infants fever and impaired mental status indicate that acute bacterial meningitis should be suspected, but the clinical findings are often more obscured with irritability, lethargy, or weakness as the only initial symptoms [27]. Bulging fontanelle may be observed, whereas neck stiffness usually is absent. Some infants present with seizures as the only symptom, whereas others may present with temperature and color changes of the skin indicating impaired circulation associated with severe sepsis and septic shock.

Initial Diagnostic Management

Blood cultures, routine chemical and hematological analyses, and arterial blood gas with analysis of lactate should be taken immediately on admission.

Lumbar puncture and cerebrospinal fluid analyses are the mainstay in diagnosing acute bacterial meningitis because it is the only method that can confirm or refute

the diagnosis [28–30]. A highly plausible diagnosis may be set "bedside" within minutes if the cerebrospinal fluid is cloudy and the spinal opening pressure is clearly elevated (>300 mmH_2O). The diagnosis may appear obvious within 1–2 h after cerebrospinal fluid analyses of leukocyte count (>500–1000 × 10^9/L with polynuclear predominance), glucose (cerebrospinal fluid/serum ratio <0.4), lactate level (>4–5 nmol/L), and/or protein level (>1 g/L). Furthermore, bacteria may be disclosed by direct microscopy and antigen detection in cerebrospinal fluid within a few hours. The final diagnosis is set by culture and/or polymerase chain reaction (PCR) on cerebrospinal fluid and/or blood within 1–3 days. Recently developed polymerase chain reaction (PCR) assays may disclose the diagnosis in less than 1 day from admission [31, 32]. The culture enables susceptibility testing of antibiotic resistance that makes it possible to adjust the antibiotic treatment.

A prompt lumbar puncture is the key to early diagnosis and adequate treatment. However, performing prompt lumbar puncture or computerized tomography (CT)-preceded lumbar puncture is a controversial issue. Some authorities recommended that, in certain situations with suspected increased intracranial pressure and/or cerebral mass lesion, such as brain abscess, the clinician should refrain from prompt lumbar puncture and instead first perform a CT of the brain, since it is argued that lumbar puncture may increase the risk of brain herniation [28–30]. However, firm evidence for a causal link between lumbar puncture and herniation is lacking, and the natural course of acute bacterial meningitis or a mass lesion/brain abscess may itself result in herniation [33–36]. Furthermore, it is shown that cerebral CT is poor at predicting the risk of herniation in acute bacterial meningitis [37–39] and that CT scan seldom contributes with valuable information in cases with suspected bacterial meningitis [40]. The importance of early antibiotic treatment is emphasized in all guidelines, and there is a strong recommendation that whenever lumbar puncture is delayed, e.g., due to neuroimaging, empiric antibiotics must be started immediately on clinical suspicion, even if the diagnosis has not been established [28–30]. Yet, antibiotics are started before neuroimaging in only 30–50% of the patients where lumbar puncture is done after the CT scan [1, 41, 42]. Thus, in clinical practice, adequate antibiotics are usually started at first when lumbar puncture has been performed and neuroimaging before lumbar puncture is associated with delayed adequate treatment and increased risk of mortality and unfavorable outcome [1, 42–44]. This evidently negative effect of performing CT before lumbar puncture outweighs the hypothetical risks with prompt lumbar puncture [34]. Guidelines differ as to when to perform neuroimaging before lumbar puncture in patients with suspected bacterial meningitis. There is consensus that CT should precede lumbar puncture if a mass lesion is more probable than meningitis, i.e., in cases with focal neurological deficit other than cranial nerve palsy and/or if long duration (>4 days) of cerebral symptoms is noticed. Some guidelines also recommend neuroimaging before lumbar puncture in cases with impaired mental status, new-onset seizures, immunocompromised state, or papilledema [28–30]. However, these findings may be present in acute bacterial meningitis as well as in cases with mass lesion, and adequate funduscopy is difficult to perform in the emergency room [28].

In adults, especially the elderly, acute bacterial meningitis is often one of many differential diagnoses at the emergency department and should be suspected in many cases. Patients with acute bacterial meningitis often need early treatment at an intensive care unit and some should be administered intracranial pressure-targeted therapy at a neuro-intensive care unit (see below) [21]. A highly plausible diagnosis of acute bacterial meningitis, accomplished only by lumbar puncture, is usually required to reach the decision to administer these advanced management modalities early after admission. The problem with delayed treatment due to neuroimaging before lumbar puncture is less pronounced in children because pediatricians usually start empiric treatment for bacterial meningitis on clinical grounds even without lumbar puncture and cerebrospinal fluid analyses [27]. Thus, prompt lumbar puncture is not as important in children as in adults. However, a rapid and firm diagnosis is desirable in severe cases also in children indicating early administration of corticosteroids, intensive care, and intracranial pressure-targeted treatment.

There are also difficulties associated with antibiotic treatment that is not delayed but started before cranial CT and lumbar puncture. One problem is the increased risk of cerebrospinal fluid sterilization resulting in negative culture results [45, 46], which make further secondary antibiotic choices more difficult and hinder decisions regarding length of treatment. Although blood cultures taken before treatment can help to identify the causal agent, positive blood cultures are noted in only 50–70% of ABM cases [1, 4]. Another problem with postponed lumbar puncture is the risk of delaying and further complicating differential diagnostics, i.e., for viral meningitis, herpes simplex encephalitis, tuberculosis meningitis, and various noninfectious cerebral conditions. This issue is of particular interest in adults, where differential diagnoses are more complex and symptoms less clear as compared with children beyond the neonatal period.

Delayed Lumbar Puncture

Lumbar puncture should not delay treatment with more than about 15 min. If technical problem with lumbar puncture, i.e., if the patient suffers from psychomotor anxiety and cannot lie still, adequate treatment for bacterial meningitis should be started immediately and then the patient should be transferred rapidly to the intensive care unit for sedation before lumbar puncture is performed. In cases with ongoing seizures, these must be treated and have subsided before lumbar puncture is performed.

In cases with primary suspicion of cerebral mass lesion, lumbar puncture should be delayed until after cerebral CT (see above and Fig. 2.1).

Lumbar puncture should not be performed promptly in cases with known bleeding abnormalities such as hemophilia and treatment with warfarin or direct oral anticoagulants (DOAC). In these cases lumbar puncture can be performed when the coagulation disorder is corrected to a level of INR <1.6 and a platelet count of $>30 \times 10^9$/L [34]. In patients on treatment with clopidogrel, lumbar puncture can be performed initially only if no signs of bleeding problems, such as mucosal bleeding

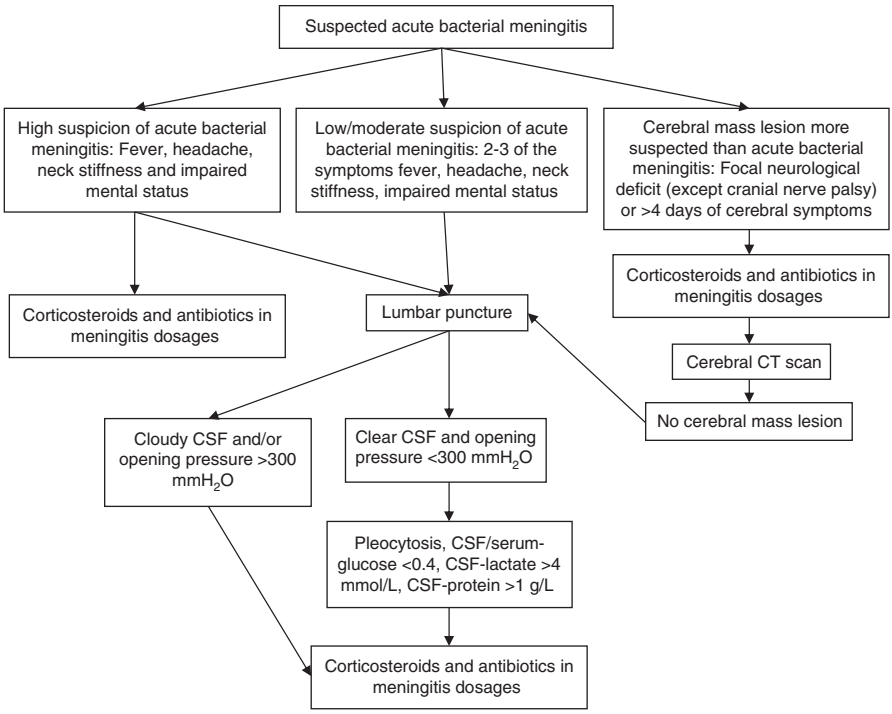

Fig. 2.1 Algorithm for diagnostic and treatment management on admission in patients with suspected community-acquired acute bacterial meningitis. *CSF* cerebrospinal fluid

from the nose, gastrointestinal or urogenital tract, or during teeth brushing, have been noticed. Patients on low molecular weight heparin can undergo lumbar puncture after 12 h (if prophylactic dose) or 24 h (if therapeutic dose) from the latest dose [28]. Lumbar puncture can be performed promptly in patients on acetylsalicylic acid or nonsteroid anti-inflammatory drugs (NSAID). Affected coagulation system associated with sepsis has not been linked with any severe risks with lumbar puncture. Thus, coagulation analyses are not required routinely before lumbar puncture in septic patients. Signs of infection at the site for spinal tap are a contraindication for lumbar puncture.

Performing Lumbar Puncture

The lumbar puncture should be performed with the patient lying horizontally on side with the back bended maximally. Funduscopy is not mandatory before lumbar puncture but should be performed if suspicion of increased intracranial pressure of long duration. The space between spinal processes L_3–L_4 or L_2–L_3 should be penetrated using a spinal tap needle with a diameter of 0.7 or 0.9 mm or with a 22 gauge needle. The opening pressure is analyzed by using a 500 mm long plastic tube that is

connected to the spinal needle directly when the cerebrospinal fluid appears in the needle. At minimum three sterile sample tubes in clear glass or plastic should be filled with about 1 mL of cerebrospinal fluid. Cerebrospinal fluid should be observed visually immediately to determine if it is cloudy or clear. The first tube should be sent to the microbiology laboratory for culture, the second stored in a fridge for virus analyses if needed, and the third should be sent immediately to the chemistry laboratory for acute analyses of cell count and levels of glucose, lactate, and protein/albumin.

In aggregate, prompt lumbar puncture should be performed liberally if acute bacterial meningitis is suspected and impaired mental status, new-onset seizures, immunocompromised state, or papilledema should not be considered indications for neuroimaging before lumbar puncture [1]. Figure 2.1 shows a recommended algorithm for diagnostic and treatment management on admission in patients with suspected community-acquired acute bacterial meningitis. In patients with high suspicion of acute bacterial meningitis, corticosteroids and antibiotics in meningitis dosages should be started regardless of cerebrospinal fluid analyses. In these cases lumbar puncture should be performed just before the start of antibiotic treatment and a sequence of corticosteroids – lumbar puncture – antibiotics is proposed.

Management in the Emergency Room

The patient should be placed in a 30° sitting position in order to decrease the elevated intracranial pressure [21]. Oxygen and slowly infused crystalloid solution should be administered. A urine catheter should be placed. Patients must be continuously observed regarding mental status with Glasgow Coma Scale (GCS) or Reaction Level Scale (RLS), circulation, urine production, and respiration. A specialist in intensive care should be contacted for early referral to intensive care unit in cases with severely impaired mental status (Glasgow Coma Scale < 12/Reaction Level Scale > 2), if deterioration of mental status is noticed, if seizures have occurred, if the spinal opening pressure is very high (>400 mmH_2O), or if septic shock is diagnosed. In septic patients arterial lactate should be reanalyzed within 3–6 h. Adequate antibiotics and corticosteroids (when indicated) should be started within 1 h from admission to hospital. Prehospital antibiotic treatment should be given if acute bacterial meningitis is highly suspected in primary care, and the referral time to hospital is estimated to be more than 1 h [28]. Cefotaxime, ceftriaxone, or penicillin G in meningitis dosages intravenously is appropriate (see below).

Empiric Antibiotic Treatment

Initial empiric antibiotic treatment should cover the vast majority of possible bacteria that may cause acute bacterial meningitis. The drug should be bactericidal and have a good penetration of the blood-cerebrospinal fluid barrier. Since the epidemiology and the bacterial resistance pattern vary between different countries and over time, the recommendations must be flexible and should be updated continuously.

In bacterial meningitis high doses of antibiotics should be administered intravenously during the entire course of treatment because the blood-cerebrospinal fluid barrier improves after a few days of treatment, and therefore the penetration into CNS is gradually decreasing.

Several older studies of ampicillin, chloramphenicol, and cefuroxime have shown good effect but are of little value today because the susceptibility pattern has changed over time and several case reports of treatment failures with these antibiotics have been presented [47]. During recent year third-generation cephalosporins has been the mainstay in treatment of community-acquired acute bacterial meningitis [7, 28–30]. Relevant randomized clinical trials (RCTs) are presented in Table 2.2 [48–58]. Two studies have shown delayed sterilization of cerebrospinal fluid with cefuroxime compared with ceftriaxone [48, 52]. Results from experimental studies in rabbit correspond well with treatment results in humans. Animal studies have, thus, been used for development and evaluation of new antibiotic strategies [47]. The bactericidal concentrations achieved in cerebrospinal fluid have been higher for cefotaxime and ceftriaxone compared with cefuroxime. Implementation of empiric treatment with cefotaxime, ceftriaxone with or without ampicillin, and meropenem is based on a few randomized clinical trials with relatively small number of patients, and most studies are performed in children, whereas few studies have included adults (Table 2.2). Relevant randomized clinical trial of treatment of neonatal bacterial meningitis is lacking. An increasing clinical experience of, especially, cefotaxime and ceftriaxone alone or in combination with ampicillin has indicated that these antibiotics are safe and have good effect in acute bacterial meningitis.

No randomized studies have been done on treatment of resistant pneumococci, meningococci with reduced susceptibility, *Listeria monocytogenes*, or other uncommon bacteria such as streptococci, staphylococci, or enterobacteriacae. In these conditions the recommendations are based on case series and case reports supported by animal studies. The incidence of *Streptococcus pneumoniae* resistant to cephalosporins has increased in some countries, whereas a very low incidence remains in many other countries.

Meropenem has showed similar effect in vitro as cefotaxime and ceftriaxone against *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* including strains of pneumococci and meningococci with reduced susceptibility to penicillin. Most gram-negatives, including *Pseudomonas aeruginosa*, and *Listeria monocytogenes* are in vitro sensitive to meropenem, but the clinical experience of this treatment is limited [59]. *Streptococcus pneumoniae* that is resistant to cephalosporins is usually also resistant to meropenem. Vancomycin has good effect against cephalosporin resistant pneumococci and other resistant gram-positive bacteria, but a drawback with this drug is that the penetration of the blood-cerebrospinal fluid barrier is not as good as for cephalosporins and many other antibiotics, especially during corticosteroid treatment. Linezolid is also effective against resistant gram-positives including cephalosporin resistant pneumococci [60]. Since the bioavailability and penetration into CNS is good, linezolid is an alternative to vancomycin, but the antibacterial action is bacteriostatic rather than bactericidal, and the clinical efficacy is not as well documented as for vancomycin.

Table 2.2 Randomized controlled studies (RCTs) of empiric antibiotic treatment of community-acquired acute bacterial meningitis

References	Studied antibiotic (*n*)	Compared antibiotic (*n*)	Study population	Main results and conclusion	Comments
[48]	Ceftriaxone (174)	Cefuroxime (159)	Children[a]	Delayed sterilization and increased hearing deficit in the cefuroxime group	
[49]	1.Chloramphenicol (53) 2. Ampicillin + chloramph (46) 3. Cefotaxime (51) 4. Ceftriaxone (50)		Children[a]	No sterilization of cerebrospinal fluid in four patients in chloramphenicol group Otherwise no difference	
[50]	Ceftriaxone (39)	Ampicillin + chloramph. (42)	Children[a] and adults	No difference	
[51]	Cefotaxime (42)	Ampicillin + chloramph. (43)	Children[a]	No difference at 4 months follow-up	
[52]	Ceftriaxone (53)	Cefuroxime (53)	Children[a]	Delayed sterilization and increased hearing deficit in the cefuroxime group	
[53]	Meropenem (98)	Cefotaxime (98)	Children[a]	No difference	
[54]	Cefepime (43)	Cefotaxime (47)	Children[a]	No difference	
[55]	Meropenem (23)	Cefotaxime or ceftriaxone (22)	Adults	No difference	
[56]	Cefotaxime (38)	Ceftriaxone (44)	Children[a]	No difference	Treatment duration 4–7 days
[57]	Meropenem (129)	Cefotaxime (129)	Children[a]	No difference	
[58]	Trovafloxacin (108)	Ceftriaxone ± vancomycin (95)	Children[a]	No difference	Trovafloxacin withdrawn due to liver toxicity

Only studies with more than 40 patients are included

[a]Excluding neonatal meningitis

There is limited experience on treatment with cefepime as an alternative; besides better activity against enterobacteriacae, no advantage compared with cefotaxime or ceftriaxone has been observed [54]. The new quinolones, levofloxacin, and moxifloxacin have broad activity against most meningitis-associated bacteria (pneumococci, meningococci, *listeria monocytogenes* and *Haemophilus influenzae*), and since they are lipophilic, they penetrate the blood-cerebrospinal fluid barrier well irrespective of barrier damage [58]. A randomized clinical trial has showed similar effect of trovafloxacin as ceftriaxone in children but trovafloxacin has been withdrawn due to liver toxicity. Levofloxacin and moxifloxacin are interesting alternatives in the empiric treatment of acute bacterial meningitis, and experimental studies indicate a synergistic action between these drugs and beta-lactam antibiotics including meropenem [61]. Moxifloxacin is recommended in favor of levofloxacin in acute bacterial meningitis due to better effect on *Streptococcus pneumoniae*. However, the clinical experience of quinolones is limited, and they should be considered second-line choice, such as in cases with allergy to penicillin and/or cephalosporins. The quinolones are often active against cephalosporin resistant pneumococci, but the antibacterial activity is not as effective as for vancomycin or linezolid. Experimental animal studies have indicated that treatment with rifampicin is associated with less inflammatory response [62], and one clinical study has showed decreased mortality in pneumococcal meningitis when rifampicin was added to cephalosporin treatment [63]. However, further studies are needed before a general recommendation can be stated.

In aggregate, cefotaxime or ceftriaxone ± ampicillin must be regarded first-line empiric treatment for community-acquired acute bacterial meningitis (Table 2.1). Ampicillin should be added if *Listeria monocytogenes* can be suspected as in the newborns, in the elderly (>50 years of age), and in immunocompromised state. In cases where uncertainty whether the patient is immunocompromised or not, ampicillin should be added to the cephalosporin. Although less documented, monotherapy with meropenem is an acceptable alternative to cefotaxime or ceftriaxone with or without ampicillin, and meropenem is indicated in patients allergic to penicillin if listeriosis must be covered. Most international guidelines recommend addition of vancomycin to cover resistant pneumococci [7, 28–30]. Local epidemiological surveillance of resistance pattern is important, and the recommendations should vary depending on the actual local incidence of pneumococcal resistance to penicillin G and cephalosporins. If the incidence of cephalosporin resistance exceeds, 1% addition of vancomycin is justified. In cases with cephalosporin/meropenem allergy, a combination of moxifloxacin and vancomycin/linezolid is recommended with addition of trimethoprim-sulfamethoxazole if listeriosis is suspected. The recommendations in different age groups are summarized in Table 2.1.

Targeted Antibiotic Treatment

The antibiotic treatment for acute bacterial meningitis should be considered in three steps. The first step is to start empiric antibiotics as stated above which should be done within 1 h from admission. The second step is to adjust initial treatment according to