Bacterial Meningitis in the ICU

36

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Case Presentation

A 55 year old man with a history of recurrent bacterial sinusitis was brought to the emergency department for 1 day of progressive confusion. The patient complained of a severe, generalized headache and light sensitivity. On exam he was febrile to 102.1 °F, agitated and oriented to name only. Severe nuchal rigidity was present, but no obvious focal neurologic deficits were observed on exam. Papilledema was not visualized on fundoscopy although the exam was limited due to the patient's significant photosensitivity.

Blood cultures were sent immediately and the patient was initiated on empiric IV antibiotic therapy with vancomycin, ampicillin, and ceftriaxone. A computed tomography (CT) of the brain without contrast did not reveal any mass lesions or obvious signs of increased intracranial pressure. A lumbar puncture (LP) was significant for an elevated opening pressure of 32 cmH_2O and CSF analysis revealed a white blood cell (WBC) count of 3000 cells/μL with 88 % neutrophils, glucose of 30 mg/dL and protein of 250 mg/dL. A gram stain showed gram positive cocci in pairs and chains (Fig. 36.1).

During transfer of the patient from the ED, the patient developed a generalized tonic-clonic seizure and was urgently given IV lorazepam. Due to decreased level of consciousness after the seizure, the patient was intubated for airway protection and was admitted to the ICU.

Question What additional inpatient precautions should be taken for the most likely diagnosis?

Answer Droplet precautions for presumed acute community acquired bacterial meningitis.

This patient presented with the 'classic triad' for bacterial meningitis of fever, neck stiffness and altered mental status (AMS). Although the

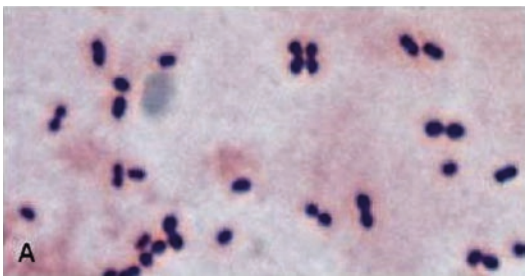

Fig. 36.1 Gram positive lancet shaped diplococcic confirming *Streptococcus pneumonia* (Image courtesy of Dr. Valerie Ng at Alameda Health System)

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complete triad is present only 44 % of the time [1], nearly all patients with bacterial meningitis will present with one of the three findings [2]. The absence of all three of these signs in the classic triad essentially eliminates bacterial meningitis from the differential [2]. The classic physical exams for evaluation of meningeal irritation, Kernig's and Brudzinski's signs are not that useful as these only have 61 % sensitivity for bacterial meningitis compared to nuchal rigidity (difficulty with chin to chest or flexion of the cervical spine) which has 84 % sensitivity for bacterial meningitis [3]. While these physical exam signs may provide support in establishing the diagnosis, a lumbar puncture is still required for definitive diagnosis.

Until the specific pathogen responsible for community acquired bacterial meningitis has been identified, strong consideration should be given for initiating droplet precautions. Droplet precautions are recommended by the CDC to decrease the spread of infection caused by *Neisseria meningitides* and *Haemophilus influenzae* type b. A definitive diagnosis may be delayed for several days [4]. In addition, depending on the quality of the gram stain, differentiating between gram positive cocci and gram negative cocci may be difficult. For these reasons, a general recommendation is to keep patients with presumed community acquired bacterial meningitis in droplet precautions for at least the first 24 h of therapy and until the etiology has been determined.

Although appropriate empiric antibiotics to cover the usual organisms implicated in community acquired bacterial meningitis were initiated, all adult patients with suspected or confirmed bacterial meningitis by lumbar puncture should also be treated with IV dexamethasone prior to or at the time of their first dose of antibiotics [1]. In our case, this patient should have be started on the standard dose of dexamethasone at 10 mg IV q6h, 15 min prior to initiation of his antibiotics to complete a 4 day course [1, 5]. The efficacy of steroids in bacterial meningitis is discussed further in the management section of this chapter.

It is critical to initiate empiric antibiotics promptly and without delay while awaiting CSF gram stain results or imaging of the brain. In this case, the patient did meet criteria for imaging prior to LP due to altered level of consciousness, (see below), still empiric antibiotics were given promptly. Initially, during selection of the antibiotics it is important to assume a high likelihood of antimicrobial resistance and select broad coverage. In this case, our patient's empiric antibiotics included vancomycin and ceftriaxone to cover for the most common pathogens, *Streptococcus pneumoniae* and *Neisseria meningitides.* Because this patient was over age 50 years, ampicillin was also appropriately added to cover for *Listeria monocytogenes.*

Although the gram positive diplococci were seen on gram stain, suggestive of *Streptococcus pneumoniae*, the patient was continued on the recommended empiric antibiotics vancomycin 15 mg/kg IV q8h (15–20 ug/mL trough target) and ceftriaxone 2 g IV q12h until definitive culture results and sensitivities are available. See Fig. 36.1.

Our patient was also started on anti-epileptic therapy and had no additional seizure activity. Over the next few days the CSF cultures grew pansensitive *Streptococcus pneumoniae* and the patient was continued on ceftriaxone for a 14 day course. By the third day the patient was alert and able to follow commands and was extubated. Seizure medications were discontinued and no further seizures occurred.

Principles of Management

Early recognition and treatment is critical to survival from bacterial meningitis. The host inflammatory response to this infection can be devastating. Several host and pathogen related factors ultimately lead to this condition. Virulence factors allow bacteria to colonize host epithelium with seeding of the bloodstream, crossing of the blood brain barrier and subsequent multiplication in the CSF due to the relative paucity of humoral immunity in the CSF. This cascade of events can lead to both systemic and neurologic complications. Here we will discuss the basic epidemiology, diagnosis, and treatment of community acquired bacterial meningitis.

Epidemiology

In recent decades there has been a shift in the pathogens responsible for bacterial meningitis. With the development and standardization of childhood vaccines against H. influenza type b (Hib) in 1985, pneumococcal vaccines (pneumococcal conjugate vaccine [PCV13] and pneumococcal polysaccharide vaccine [PPSV23]) in 2000 and meningococcal conjugate vaccine (MCV4) in 2005 the burden of bacterial meningitis has shifted to predominately older populations [6, 7]. Despite vaccines, *Streptococcus pneumoniae* and *Neisseria meningitidis* still account for over 80 % of bacterial meningitis cases [7, 8]. Less common pathogens, *Group B Streptococcus* (GBS), *Haemophilus influenzae Listeria monocytogenes* make up the remaining approximately 17 % of cases [7]. Patients' ages 16–50 are at greatest risk for *Neisseria meningitidis* or *Streptococcus pneumoniae,* however, patients over the age of 50 or immunocompromised patients have an increased risk for *Listeria monocytogenes,* GBS, and aerobic gram negative bacilli [7, 8].

Diagnosis

All patients with suspected bacterial meningitis should receive an LP unless contraindicated. See Fig. 36.2 for a management algorithm in all patients with suspected bacterial meningitis. Relative contraindications include elevated intracranial pressure, thrombocytopenia/bleeding diathesis or spinal epidural abscess [10]. If collection of CSF is delayed for imaging or other reasons, blood cultures should be collected prior to antimicrobial administration but antibiotics should not be delayed. Positivity of blood cultures for bacterial meningitis range from 50 to 90 % [1].

CSF results consistent with the diagnosis of bacterial meningitis include (1) elevated opening pressure (normal 20cmH2O), (2) pleocytosis of 1000 to 5000 μL with a >80 % neutrophil predominance, (3) glucose below 40 mg/dL (in adults glucose ratio CSF: serum ≤0.4), (4) mildly elevated protein level 100–500 mg/dL and (5) cloudy or turbid appearance.

Sensitivity for a positive gram stain ranges from 60 to 90 % with a >97 % specificity; greater likelihood of positive gram stains are seen in streptococcus pneumoniae, H. flu and Neisseria as opposed to gram negative bacilli [11]. See Table 36.1. CSF cultures identify an organism 70 to 85 % of the time [13]. Serum and urine bacterial antigens are not routinely helpful.

Notably, a traumatic tap, intracerebral or subarachnoid hemorrhage or recent seizure can all result in a falsely elevated WBC in the CSF. To correct WBC for a traumatic tap, subtract 1 WBC for every 500 to 1500 red blood cells (RBCs) in CSF to give the 'Adjusted CSF WBC' [14].

Select patients may be at risk for undergoing an LP and should receive imaging prior to LP. Antibiotic administration, however, should not be delayed [15]. See Fig. 36.2.

Repeat LPs are not indicated in patients with bacterial meningitis unless there has been no clinical improvement after 48 h of appropriate antibiotics. This is especially important if there is concern for pneumococcal meningitis with penicillin or cephalosporin resistance or when the patient has been treated with dexamethasone [1].

Antibiotics

A delay in administration of antibiotics of greater than 3 h from admission in bacterial meningitis has been associated with increased morbidity and mortality. Antibiotics should target the presumed pathogen identified by gram stain, or empirically started if the LP is delayed [1]. Antibiotics should be bactericidal and cross the blood brain barrier [16].

Empiric antibiotics for adults are vancomycin and a third generation cephalosporin (ceftriaxone or cefotaxime). In patients with risk factors for listeria (>50 years old, immunocompromised or alcoholism) the addition of ampicillin or penicillin G should be included. If there is a beta-lactam allergy: Vancomycin and moxifloxacin are considered empiric coverage with trimethoprim-sulfamethoxazole added for listeria. Consider the use of a fourth generation cephalosporin such as cefepime or a carbapenem such as meropenem in

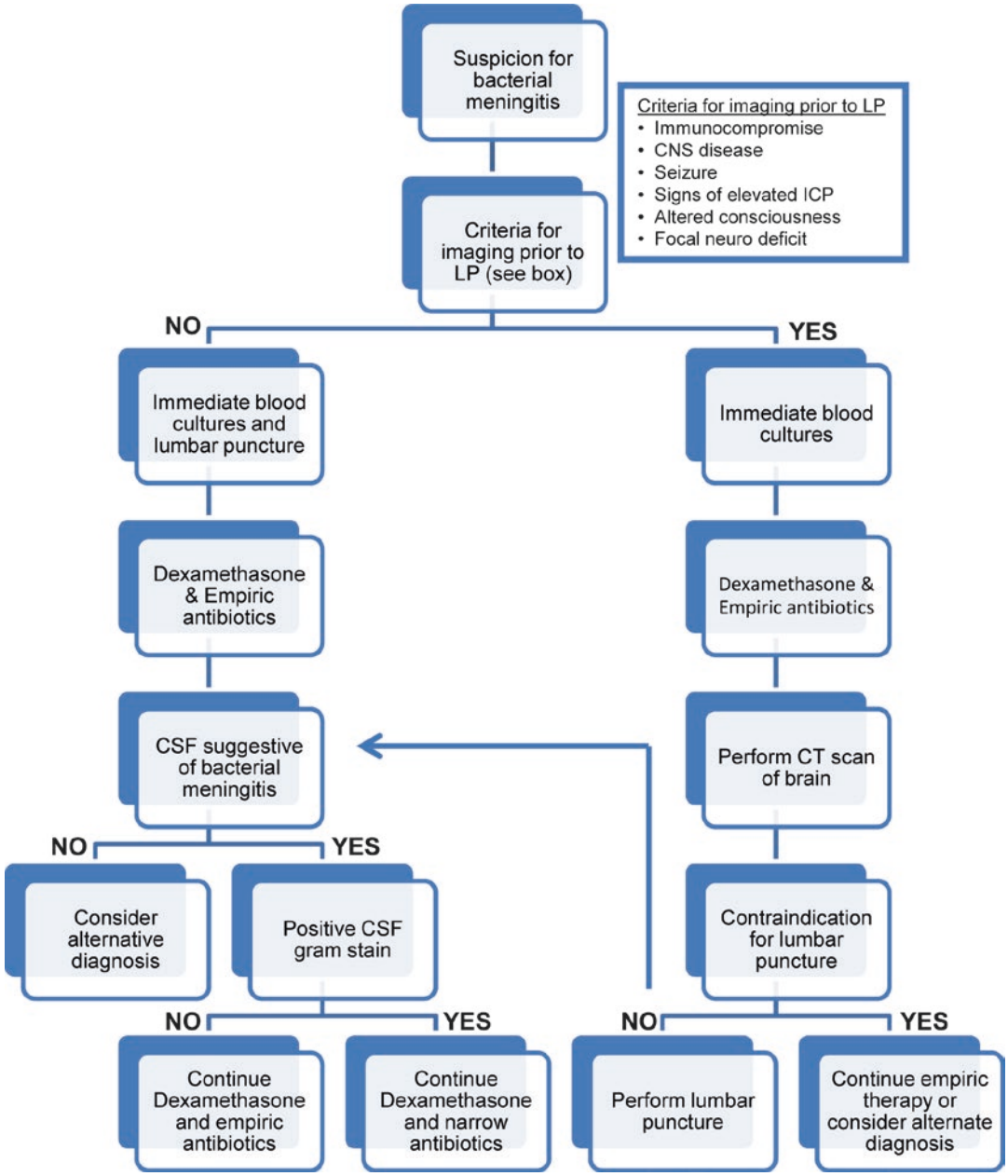

Fig. 36.2 Management algorithm for adults with suspected bacterial meningitis [9] (From Tunkel et al. [9]. Reprinted with permission from Oxford University Press)

severely immunocompromised patients to cover for additional gram negative pathogens.

The duration of antibiotic therapy is usually from 7 to 14 days but should be guided by the specific pathogen identified, disease severity and antimicrobial agent selected [9, 17, 18] See Table 36.2.

Steroids

Dexamethasone works via two routes: (1) reduction in meningeal inflammation (2) blunting a secondary inflammatory response to the bacterial products released from the first dose of antibiotics

[17]. Optimal initiation of dexamethasone is 15 to 20 min prior the first dose of antibiotics, or alongside their first dose of antibiotics. The recommended dose of dexamethasone is 0.15 mg/kg IV every 6 h [4]. The administration of dexamethasone in patients with bacterial meningitis reduces unfavorable neurological outcomes. Notably, the reduction in mortality was only statistically significant in patients presenting with a moderate level of neurological impairment at admission (Glasgow Coma Scale [GCS] score of 8 to 11). No benefit to mortality was seen if the patients with GCS scores > 11. No proven benefit and a higher likelihood of poor outcomes have been identified if dexamethasone is given after antibiotics have been started [4].

The reduction in neurologic sequelae and mortality with adjunctive steroids are clearly seen with pneumococcal meningitis. Unfortunately these findings have not been proven in meningitis caused by other pathogens. Nevertheless, the Infectious Diseases Society of America (IDSA) recommends adjunctive dexamethasone in all adult patients with suspected or proven bacterial meningitis.

Table 36.1 Gram stain appearance for specific bacterial meningitis pathogens [12].

Gram stain appearance	Specific pathogen
Gram positive diplococci 'lancet-shaped'	***Streptococcus pneumoniae***
Gram positive cocci in clusters or tetrads	***Staphylococcus aureus***
Gram positive cocci	***Streptococcus agalactiae***
Gram positive rods	***Listeria monocytogenes***
Gram negative diplococci	***Neisseria meningitidis***
Pleomorphic gram negative rods (cocco-bacilli)	***Haemophilus influenzae***
Gram negative rods	***E. Coli* or other *Enterobacteriaceae***
Gram negative rods (bacilli)	***Pseudomonas aeruginosa***

Long Term Neurologic Complications

The risk of developing any neurologic complications has been sited to be as high as 28 % overall in community acquired bacterial meningitis and depends on the pathogen involved,

Table 36.2 Recommended antibiotic duration for specific bacterial meningitis pathogens [1]

Specific pathogen	Antibiotics	Duration
Strep pneumoniae		
PCN		
MIC < 0.06 mcg/mL	Penicillin G (monotherapy)	10–14 days
MIC ≥ 0.12[a]	3rd generation cephalosporin[b]	
If Ceftriaxone MIC > 1 mcg/mL	Add Vancomycin	
Neisseria meningitidis	3rd generation cephalosporin[b]	7 days
Haemophilus influenzae		7 days
Beta-lactamase NEG	Ampicillin	
Beta-lactamase POS	3rd generation cephalosporin[b]	
Listeria monocytogenes	Ampicillin or Penicillin G	21 days
Streptococcus agalactiae	Ampicillin or Penicillin G	14–21 days
	Plus aminoglycoside	
***E. Coli* or other Enterobacteriaceae**[a]	3rd generation cephalosporin[b]	14–21 days
Pseudomonas aeruginosa[a]	Cefepime or ceftazidime	21 days
Staphylococcus aureus		
Methicillin susceptible	Nafcillin or oxacillin	10–14 days
Methicillin resistant	Vancomycin	

MIC minimum inhibitory concentration
[a]Add rifampin if MIC >2 mcg/mL for 3rd generation cephalosporin to maximize CSF penetration.
[b]Ceftriaxone or cefotaxime

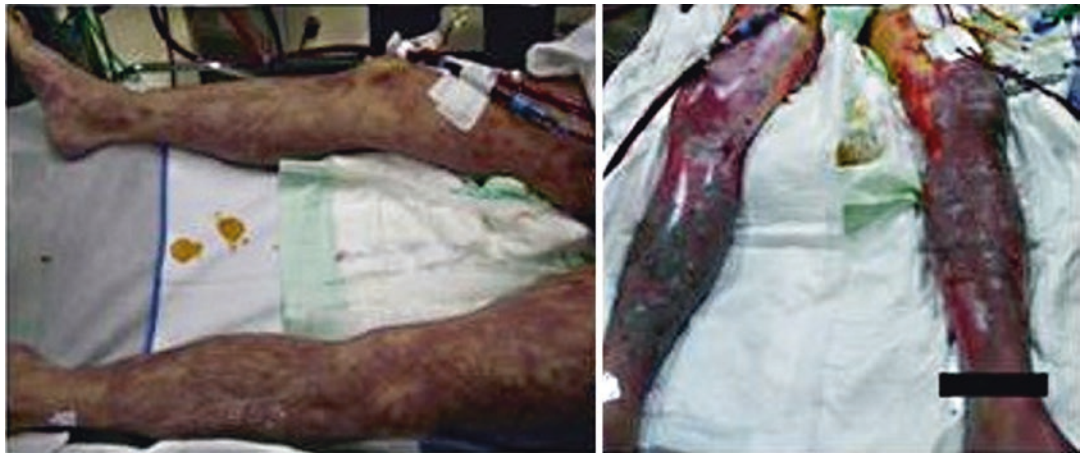

Fig. 36.3 Examples of purpura fulminans (From Endo et al. [24]. Courtesy of Biomed Central (Open Access))

time to antibiotic administration, severity at presentation, and whether steroids were administered [19]. Neurologic complications include both early onset (altered mental status, elevated ICP, seizures, focal neurologic deficits) and more long term sequelae (permanent neurologic deficits, hearing loss, or cognitive impairment). One study examined a model for prediction for neurologic complications or death at discharge using hypotension, altered mental status, and seizures as criteria. The presence of 2 of the 3 criteria predicted a 56 % chance of adverse outcome, while the presence of only 1 of the 3 criteria predicted a 9 % chance of adverse outcome. It was also noted that neurologic events were seen more in pneumococcal meningitis [17].

Meningococcemia

It is important to briefly discuss additional specific details related to *N. meningitidis* and the development of meningococcemia. *N. meningitidis* can cause three major syndromes: meningitis alone; meningitis accompanied by meningococcemia (sepsis); or meningococcemia without meningitis. In these disease states caused by *N. meningitidis,* mortality is higher and timely antibiotics are crucial with an antibiotic delay of even 30 min considered unacceptable [20].

Meningeal signs and symptoms along with fever and petechial rash should immediately prompt a suspicion for *N. meningitidis* and the possibility of meningococcemia. An additional nonspecific clue includes the presence of myalgias which are not often seen with pneumococcal meningitis and are typically more severe than the myalgias seen with influenza. Neisseria infections often occur in outbreaks in the late winter and can present similarly to the flu with nonspecific URI symptoms preceding more serious symptoms which can develop within a matter of hours. A key clinical feature to be aware of with meningococcal infection is a rash which can be petechial or hemorrhagic and is seen in about half of all cases [21]. This rash usually is more prominent in the trunk and lower extremities and at sites where pressure is applied to the skin such as belts or elastic bands [22]. Mucous membranes of the soft palate and eye must also be examined for signs of hemorrhage. The lesions are usually 1 to 2 mm in diameter and can coalesce into larger patches. The severity of the rash is directly proportional to the overall severity of illness including the presence of shock and disseminated intravascular coagulation (DIC). The devastating complication of purpura fulminans is seen in 15–25 % cases [23]. See Fig. 36.3. The cascade of organ dysfunction seen in meningococcemia – coagulopathy, DIC, acute respiratory distress syndrome (ARDS), sepsis, purpura fulminans

and adrenal shock (Waterhouse-Friderichsen syndrome) are initiated in large part by the lipooligosaccharide, a potent toxin in the bacterial meningococcal membrane [25].

A key management principle in meningococcal infections is the prevention of spread to others. Importantly, droplet precautions should be started as soon as possible in all cases of community acquired bacterial meningitis and should be continued until meningococcal and/or haemophilus infection has been ruled out. In cases with confirmed meningococcal infection consideration for post-exposure prophylaxis should be given (see evidence contour section).

Evidence Contour

ICP Management

Elevations in intracranial pressure (ICP) are commonly seen in bacterial meningitis and are thought to be related to the development of permanent neurological problems such as deafness, epilepsy and poor cognition [26]. Reducing infection-induced swelling (vasogenic edema) is a goal to improve outcomes. In addition to antimicrobial therapy, initial medical management of elevated ICP from meningitis includes general measures (1) elevating head of bed >30° with head in neutral position to avoid jugular vein compression, (2) maintenance of normothermia, (3) avoidance of hypotension/hypovolemia (4) hyperventilation, and (5) mannitol [26]. While monitoring of ICP is not standard of care in bacterial meningitis, it may be considered in patients with a GCS < 8 and the gold standard for monitoring ICP involves the placement of an intraventicular catheter. Other osmotic therapies such as the use of glycerol have been evaluated for ICP management in bacterial meningitis but have not shown benefit in adults [27, 28].

Hypothermia

Therapeutic hypothermia has known neuroprotective benefits following cardiac arrest. Hypothermia as adjunctive therapy in the management of bacterial meningitis has yielded inconsistent and potentially harmful results in regard to both mortality and neurologic outcomes [29, 30]. The exclusion of patients who received dexamethasone in some of the studies leads to an unclear conclusion regarding the addition of therapeutic hypothermia in bacterial meningitis patients [29]. At this time we do not recommend therapeutic hypothermia in the setting of bacterial meningitis.

Gram-Negative Bacilli Meningitis

Gram negative bacilli (GNB) meningitis occurs most frequently in neonates and infants, however, there are two additional patterns of infection: nosocomial GNB meningitis (in the setting of head trauma or neurosurgery) and spontaneous, community acquired GNB meningitis, (typically from another source of infection, such as a urinary tract infection). The incidence of nosocomial GNB meningitis is on the rise secondary to more complex neurosurgical operations and routine prophylactic antibiotics given to prevent surgical site infections [31].

Patients who present with spontaneous GNB meningitis are typically elderly or have comorbidities including cancer, diabetes, cirrhosis, immunosuppression, or splenectomy [32]. The most common pathogens are Escherichia coli (38%) and Pseudomonas species [32]. GNB meningitis presents less often with the classic meningitis triad and is associated with more neurological and systemic complications than other causes of bacterial meningitis and carries a higher mortality rate [32].

Shunts and Other Intracranial Devices

CSF shunts increase a patients risk for bacterial meningitis. Internalized shunts (draining to the peritoneum, commonly ventriculoperitoneal or VP shunt) have an infection rate of 5–15%, with an infection most common in the first month of placement. External devices such as a ventriculostomy catheter or an Ommaya reservoir (access for

administration of chemotherapy or antibiotics) may also develop infections [33]. Clinical presentation may be subtle and result from obstruction of the shunt with symptoms consistent with elevated intracranial pressure (headache, nausea and vomiting, somnolence and altered mental status). In contrast to community acquired bacterial meningitis, nuchal rigidity tends to be absent, as there is no communication between the infected ventricles and the meninges.

Evaluation still requires blood cultures, CSF cultures and imaging. However, interpretation of the CSF is more complex and cannot be made on a single parameter. Repeated positive CSF cultures over several days will help confirm the diagnosis [34]. Shunt removal is indicated to ensure treatment success [9].

Post Exposure Prophylaxis

Not all bacterial meningitis pathogens require post exposure prophylaxis for contacts to minimize spread, however both *Neisseria meningitidis* and *Haemophilus influenzae* do.

Individuals who require prophylaxis for meningitis are (1) close contacts (household members, daycare workers, military), (2) travelers in direct contact with respiratory secretions or close proximity to index patient for >8 h flight, and (3) individuals in close contact with respiratory secretions (including kissing, mouth to mouth resuscitation and endotracheal intubation). Prophylaxis should occur in a timely manner, ideally within <24 h of exposure. Prophylaxis should be given to appropriate individuals several days after exposure, however the CDC does not recommend prophylaxis >14 days after exposure [35]. Eradication of nasopharyngeal carriage is performed in outbreak settings and for the index patient (if they did not receive ceftriaxone), prior to discharge to prevent further transmission [36].

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