CASE 9.7
Meningitis | Level 3

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1. What subjective and objective evidence support the diagnosis of bacterial meningitis in this patient?

SUBJECTIVE FINDINGS: The patient presented with a chief complaint of fever (39.1°C) and irritability for the past 3 days. Early this morning, she vomited and became lethargic and is now difficult to arouse. Young children with meningitis often present with nonspecific symptoms, which can lead to misdiagnosis.

OBJECTIVE FINDINGS: On physical exam, she is febrile (39.7°C in ED), lethargic, and irritable during examination, particularly during the neck exam. The lumbar puncture results that are suggestive of bacterial meningitis are hazy color, low glucose (cerebrospinal fluid (CSF) to serum ratio ≤0.4), elevated protein, and leukocytosis with a predominance of neutrophils. This patient has evidence of a traumatic spinal tap (RBC >100,000/mm^3), which can cause xanthochromia and falsely elevate the protein and WBC count in the CSF sample. For every 1,000 RBCs in the CSF caused by a traumatic tap, there is an artificial increase of one WBC and 1 mg/dL of protein. After correcting for these values in this patient, the WBC and protein counts are still elevated and suspicious for bacterial meningitis. Other laboratory features that suggest a serious bacterial infection in this patient include hyperglycemia, metabolic acidosis, an elevated peripheral WBC count with a left shift, an elevated procalcitonin, and an elevated C-reactive protein.

Key diagnostic information used to elucidate the cause of meningitis is the Gram stain and culture of the CSF. Because this child's symptoms are consistent with meningitis, a CSF sample was obtained. The CSF Gram stain was negative, and the culture is pending. It should be noted that this patient received three doses of amoxicillin prior to the lumbar puncture obtained in the emergency department. Antibiotic pretreatment, whether oral or parenteral, can affect the positivity rate of blood and CSF cultures in children with bacterial meningitis, whereas Gram stain results do not appear to be significantly affected. However, Gram stain has a fairly low sensitivity rate (67%) for detecting bacterial meningitis and cannot be used alone to exclude infection. Other tests that may be performed to determine the cause of infection include latex agglutination and polymerase chain reaction, particularly in children who have been pretreated with antibiotics before a CSF sample was obtained or whose Gram stain and culture results are negative.

2. Develop a treatment plan for this patient's meningitis.

It is important to distinguish between bacterial and viral meningitis in order to minimize morbidity and mortality while avoiding unnecessary antibiotic use. Once it is determined that bacterial meningitis is present or until it can be ruled out when a bacterial cause is suspected, empiric antibiotic therapy is required as soon as clinically possible. The empiric regimen that is selected should be based on patient age and other clinical characteristics, such as predisposing conditions, immunization status, medication allergies, and geographical antimicrobial susceptibilities. In children 1 to 23 months of age, the most common bacterial pathogens are *Streptococcus pneumoniae*, *Neisseria meningitidis*, *H. influenzae*, *Streptococcus agalactiae*, and *Escherichia coli*, where the latter two are less common after 2 months of age. Universal childhood immunizations introduced in developed countries have nearly eradicated *H. influenzae* type b (Hib) meningitis and dramatically reduced invasive disease caused by vaccine serotypes contained in the 7-valent pneumococcal conjugate vaccine (PCV-7). Non-PCV-7 serotypes are now the leading cause of bacterial meningitis in this age group; however, PCV-7 was replaced by the 13-valent pneumococcal conjugate vaccine (PCV-13) in 2010. Its use may impact the prevalence of pneumococcal meningitis, and its effect must be monitored through epidemiologic surveillance studies. In young children, meningococcal meningitis is most commonly caused by serogroup B for which no currently licensed vaccine is available in the United States but is approved for use in Europe, Australia, and Canada. Outbreaks of serogroup B meningococcal disease at the University of California, Santa Barbara, and Princeton University in 2013 and 2014 prompted the FDA to allow emergency use of the meningococcal B vaccine for at-risk students and staff.

Based on this child's age and lack of vaccinations, the most likely causative organisms are *S. pneumoniae* and *N. meningitidis*. Although she has not been vaccinated against Hib, near complete eradication of this pathogen in the United States and protection from herd immunity make this organism a less likely cause of her infection. In addition, she has a recent history of AOM, which can lead to meningitis, particularly when caused by pneumococci. Therefore, she should receive empiric antibiotic therapy that covers both pneumococci and meningococci. The Infectious Disease Society of America (IDSA) treatment guidelines recommend initiation of parenteral vancomycin plus either cefotaxime or ceftriaxone in order to provide adequate coverage for potentially drug-resistant pathogens. Ceftriaxone is contraindicated in neonates who are hyperbilirubinemic or who require calcium-containing intravenous fluids, and it should be used with caution in patients with concurrent hepatic dysfunction and significant renal disease or patients with presence of or risk factors for biliary stasis or sludging. The goals of treatment are to eradicate the infecting organism and to prevent or manage complications. This patient should be monitored for improvement (normalization of vital signs, return to baseline mental status and behavior, and normalization of laboratory values including WBC count, procalcitonin, and CRP) and the development of complications such as seizures and hearing loss. She should also be monitored for medication adverse reactions including hypersensitivity and renal dysfunction. Repeat lumbar puncture is recommended if there is a lack of improvement or worsening after 48 hours of appropriate antibiotic therapy, in patients with pneumococcal meningitis caused by penicillin- or cephalosporin-resistant strains (particularly if dexamethasone was administered), and in neonates with meningitis caused by gram-negative bacilli.

For this patient, intravenous vancomycin 15 to 20 mg/kg/dose (150 mg) every 6 hours and intravenous ceftriaxone 50 mg/kg/dose (480 mg) every 12 hours can be initiated. If CSF culture and sensitivity results allow, antimicrobial therapy can be narrowed to treat the specifically identified pathogen. If vancomycin therapy will be continued for more than 48 hours, a target vancomycin trough of 15 to 20 mcg/mL is recommended. The duration of antibiotic therapy is dependent on the causative pathogen: a 7-day treatment course is recommended for meningococcal and *H. influenzae*

meningitis while a 10- to 14-day course is recommended for pneumococcal meningitis.

Another issue to address that is related to meningitis is this patient's lack of immunization, which predisposes her to these serious infections. Healthcare providers must investigate why she has not been vaccinated and attempt to convince her parents that she should be immunized. If her parents agree to have her vaccinated, she should receive the following vaccines once she is no longer acutely ill: hepatitis B vaccine; diphtheria, tetanus, and pertussis vaccine; Hib vaccine; PCV-13; inactivated poliovirus vaccine; measles, mumps, and rubella vaccine; varicella vaccine; and hepatitis A vaccine. She is also a candidate for an annual influenza vaccine. The catch-up immunization schedule that is approved by the Advisory Committee on Immunization Practices should be consulted for recommendations on vaccine timing for the vaccines that require a dosing series (http://www.cdc.gov/vaccines/acip/index.html).

3. Assess the use of dexamethasone for this patient's meningitis.

Neurologic sequelae resulting from meningitis occur in up to 49% of children despite antibiotic treatment, ranging from behavioral disorders to seizures and loss of hearing or vision. The presence of bacteria and the host immune response lead to neuronal damage, inflammation, thrombosis, cerebral edema, and increased intracranial pressure, all of which are further aggravated by bacterial lysis from antibiotic therapy and the ensuing inflammatory response. Dexamethasone has been studied in children with meningitis to see if anti-inflammatory therapy can reduce brain injury and mortality. A meta-analysis of eighteen randomized controlled trials in children found no effect of dexamethasone on mortality, but a subgroup analysis revealed significant reductions in hearing loss in children infected with Hib and children treated in high-income countries regardless of the infecting pathogen. The IDSA guidelines recommend the use of adjunctive intravenous dexamethasone (0.15 mg/kg/dose every 6 hours for 2 to 4 days) in children with Hib meningitis when it is initiated 10 to 20 minutes before or along with the first dose of antibiotics. Despite the lack of strong evidence to support its use in pneumococcal disease, dexamethasone use should be considered for children with pneumococcal meningitis after weighing the potential benefits and risks of therapy. Potential risks include adverse reactions, such as gastrointestinal effects and hypertension, and reduced antibiotic penetration to the site of infection, although studies have not confirmed this phenomenon. There is no evidence to support the use of dexamethasone in meningococcal meningitis.

In this patient, dexamethasone therapy could be considered because the causative pathogen is unknown (Gram stain of CSF was negative; culture is pending) and she has not received any vaccines. However, initiation of corticosteroid therapy is recommended with the first dose of antibiotics or 10 to 20 minutes before the first dose is given. This patient has not yet received parenteral antibiotics, but she received oral antibiotics prior to her presentation, which could interfere with the ability to identify the infecting pathogen. Her case could be considered a "partially treated" meningitis given the doses of amoxicillin prior to admission and data to support the protective effect of corticosteroids when given after antibiotic therapy are lacking. The IDSA guidelines recommend avoiding dexamethasone in patients who have already received antibiotics because it is unlikely to improve outcomes. Therefore, the use of dexamethasone for this patient is not recommended and it should be discontinued.

4. Provide pertinent education for the parents regarding the prognosis and long-term outcomes for children with meningitis.

Response to treatment (improvement in vital signs and neurologic status) is usually evident within 48 hours of initiating antibiotic therapy. Therapeutic failure may occur because of inadequate antibiotic treatment, development of nosocomial infection, or development of suppurative complications such as subdural empyema. For children who are not improving or are worsening, it is recommended to repeat a lumbar puncture, particularly in cases of

pneumococcal meningitis caused by penicillin- or cephalosporin-resistant strains and in those who received adjunctive dexamethasone therapy. Continued presence of infection after 48 hours of antibiotic therapy is associated with poor outcome. In these cases, changes in antibiotic selection, dosing, or duration may be necessary.

As discussed previously, meningitis can result in neurologic sequelae in almost 50% of children despite prompt and appropriate antibiotic therapy while mortality rates are much lower at approximately 2%. Certain factors, such as young age (<12 months), delayed presentation, presence of seizures or coma, need for vasopressors, and pneumococcal etiology, can increase the risk of poor outcomes. Prompt administration of antibiotics in children with a likely diagnosis of bacterial meningitis is recommended in order to minimize mortality but little evidence exists to show that it significantly reduces morbidity. After the infection has been adequately treated, some neurologic deficits may improve or resolve over time, but subtle deficits can be initially overlooked and may affect survivors for years. Thus, it is important for children to undergo vision and hearing testing along with routine primary care visits and neurologic follow-up to monitor for complications.

5. Discuss the medication-related problem in this patient and provide a recommendation for its management.

The medication-related problem was the inappropriate amoxicillin dose for this patient's weight. High-dose amoxicillin (80 to 90 mg/kg/day divided twice daily) is the first-line treatment for children with AOM. This patient was diagnosed with AOM 3 days prior to admission and was prescribed amoxicillin 800 mg twice daily as an outpatient. This dose is too high for this patient's weight (167 mg/kg/day); an appropriate dose is 400 mg twice daily. The patient has evidence of middle ear effusion but no current evidence of inflammation; despite this, antibiotic therapy for AOM should be continued for a full treatment course as this case may represent a partially treated infection. The parenteral antibiotic therapy that is recommended for meningitis (ceftriaxone plus vancomycin) will also treat the AOM, so the amoxicillin can be discontinued. A 3-day course of ceftriaxone is an appropriate alternative treatment for AOM, and it is likely that this patient will receive 7 to 14 days of parenteral antibiotics for meningitis.

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