



Midnight Madness: A crazy psychologist in the ED late at night

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A 53-year-old woman arrived in the ED late at night. Her partner was concerned that she suddenly was not acting “right.” The patient had complained of headache throughout the day but did complete her work schedule as a school psychologist and went to evening choir practice. She felt ill and went to bed early complaining of a headache. She awakened in the late night hours and seemed confused, repeating words, and not clearly recognizing her partner. EMS was called and she was transported to the emergency department.

Meaningful history could not be obtained from the patient and her partner was the initial historical source. The patient did not smoke and drank only occasionally. She reportedly did not use illicit drugs. Her past medical history was unremarkable and did not include a history of headaches. She was post-menopausal and took daily estrogen replacement therapy but no other medications. Surgical history was unremarkable except for a distant history of “sinus surgery.” Family history was non-contributory. She had no known allergies and there were no known recent sick contacts.

Physical examination showed a confused woman who responded to questions only with monosyllabic, unintelligible responses. Airway was open and intact. Pulse was 108, BP 149/-, respirations 18/minute, and oxygen saturation of 97% on room air. Temperature was 38.3. The patient could not cooperate with physical examination. The patient moved all extremities and no facial asymmetry was seen. Pupils were equal, 4 mm, and reacted briskly to light. There were no skin rashes. Chest was clear and abdomen seemed soft. It was impossible to judge neck stiffness or other signs. The patient could not localize painful stimuli.

With the fever and altered mental status, the possibility of a CNS infection was considered. Intravenous access was established and the patient received 2 grams ceftriaxone following laboratory work and blood cultures. CT showed sinus disease but no intracranial abnormalities. The LP was cloudy; the patient then additionally received acyclovir and vancomycin and was admitted to the ICU.

Key Clinical Questions

When should a CNS infection be considered in the differential diagnosis?

What is optimal timing of imaging, procedures, and therapy in patient with suspected CNS infection?

What empiric therapy should be given in the adult with possible bacterial meningitis?

What adjunctive therapy should be administered?

Key Learning Points

- The initial management of acute bacterial meningitis is clearly the province of the emergency physician and initial therapy should not be delayed pending imaging, consultation, or lumbar puncture.
- When the diagnosis is established or at the time it is strongly suspected, empiric antibiotics based on patient age and other risk factors should be administered.
- Currently, administration of dexamethasone (10 mg in adults; 0.15 mg/kg children) is recommended in most cases either moments before or at the time of antibiotic administration.

Acute Bacterial Meningitis

Background, Risk Factors and Epidemiology

Acute bacterial meningitis has long been known to be a serious and often fatal disease; it was universally fatal prior to the introduction of antibiotics. Current estimates of mortality in acute meningitis caused by *S. pneumoniae* are still on the order of 20%-25% in developed countries. The majority of cases are due to three organisms: *H. influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitidis*. The frequency of meningitis due to *H. influenzae* has dramatically dropped in the US with widespread vaccination programs. At the extremes of age other organisms are encountered, notably group B streptococcus (*S. agalactiae*) in neonates and *Listeria monocytogenes* in infants and the elderly. (1) Risk factors for community-acquired meningitis in adults include diabetes mellitus, otitis media, pneumonia, sinusitis, and alcohol abuse. (2)

The emerging penicillin resistance of *S. pneumoniae* has altered the approach and therapy to meningitis. Isolates differ around the world with penicillin resistance varying from 0-40%. In one study from Australia, resistance increased from 0% to 20% during the 5-year study period in the late 1990's. (3) This has led to the approach of assuming that penicillin resistance is present and covering with additional antibiotics (vancomycin) until culture results are available.

Anatomy and Pathophysiology

Acute bacterial meningitis may be thought to develop in several stages. Although some cases of bacterial meningitis develop from direct extension, in most cases the organism first proliferates within the nasopharynx, a state known as colonization. Infection implies invasion or proliferation in tissues; the infection may be asymptomatic (subclinical) or may cause symptoms (disease). It is interesting to note that of the many thousands of bacteria that have the potential to produce meningitis, only a few commonly produce the syndrome of acute meningitis.

Following colonization, a bacteremia may occur following microbial invasion of the intravascular space and bacterial survival and multiplication. Meningitis follows with live bacteria breaching the blood-brain barrier, surviving and multiplying in the subarachnoid space. Host immune responses ensue with reactions of disruption of the blood-brain-barrier and vasculitis with the resulting cerebral edema and neuronal injury.(4)

The blood-brain-barrier (BBB) is a structural and functional barrier formed by brain microvascular endothelial cells. Generally, the BBB excludes circulating microbes and toxins. There seems to be a threshold level of bacteremia required for meningeal invasion. Bacterial binding to the microvascular endothelial cells and invasion involve bacterial surface proteins. Once bacteria enter the CNS through the bloodstream, they multiply and induce the release of inflammatory and toxic compounds that result in pleocytosis, further BBB permeability, and neuronal damage. Neuronal injury results from many microbial and host factors; one current goal is attenuation of these specific host responses without adverse effects on other immunological functions. (4)

A vicious cycle of pathophysiologic responses may develop with endothelial cell injury and dysfunction leading to loss of cerebrovascular autoregulation, increased permeability of the BBB, development of cerebral edema, and decreasing cerebral perfusion. (5)

ED Presentation

Acute bacterial meningitis has an imperfect triad of presentation – fever, neck stiffness, and altered mental status- but this triad is fully present in less than two-thirds of patients. (2)

The classic physical examination findings of Kernig’s sign (pain in the posterior thigh or back when the knee is extended, or resistance to knee extension) and Brudzinski’s sign (passive neck flexion produces flexion of the knees and hips in the supine patient) were described in the pre-antibiotic era and likely reflect advanced cases. These classic tests for meningeal irritation are thought to be insensitive but specific for meningitis. (6) In a prospective study of adults with suspected meningitis, Kernig’s and Brudzinski’s signs were found lacking and a plea was made for better bedside diagnostic tests. (7) A test that may be better-though the study population is small-is the finding of “jolt accentuation of headache.” The patient is asked to turn his head to the left or right at a frequency of 2-3 times per second; a positive test is a subjective report of increased headache but most positive results are said to be evident to the observer. This is thought to be more sensitive than the other bedside tests of meningeal irritation, but again, study size is small. (6),(8)

Meningococcal meningitis may be associated with a petechial or purpuric rash reflecting accompanying systemic vasculitis.

Lab Studies

As with any critically ill patient, multiple laboratory studies will be obtained. With establishment of intravenous access, it is usual to obtain a CBC, serum chemistries, coagulation studies, and blood cultures, though none of these will guide decision to treat or the type of therapy.

CSF sampling confirms the diagnosis and guides therapy with culture results. The typical CSF formula of the patient with acute bacterial meningitis is the presence of leukocytes of segmented forms. Lymphocytic predominance of CSF suggests but is not conclusive of a viral or fungal infection. Elevated CSF protein is common in meningitis of any type. Low CSF glucose (two thirds or less of the serum glucose) is suggestive of bacterial infection as is an elevated CSF lactate. (8) At times, though the CSF may be clearly inflammatory, it may be inconclusive as to whether the infection is bacterial or viral. Bacterial antigens, if available, may be helpful as may PCR testing for HSV (Herpes simplex virus) in selected cases. Gram stain is commonly obtained and may show bacteria suggesting a causative organism.

Imaging Studies

Controversy continues about the need for cranial CT prior to lumbar puncture in cases of suspected acute bacterial meningitis. The fear is the theoretical risk of cerebral herniation if lumbar puncture is performed in the presence of a mass lesion such as cerebral abscess. This must be weighed against the therapeutic delays inherent in obtaining imaging and interpretation. No consensus exists on this point and there are proponents and opponents on each side with no randomized studies to tip the argument to one side. Retrospective studies have shown that delays in antibiotic administration are physician-generated and often involve imaging studies. One clinical axiom has emerged—**do not delay antibiotics in cases of suspected bacterial meningitis pending imaging studies**. If cranial CT is to be pursued, empirically determined antibiotics (and perhaps steroids) should be administered to the patient to avoid delay in initiating therapy.

Procedures

The unequivocal way to establish meningitis is to sample the CSF or the meninges themselves; except in rare instances, lumbar puncture is the means to sample the CSF. Typically, noncontrast cranial CT scanning is performed. One expert recommendation is that in cases of suspected acute meningitis, LP may be safely performed except in patients with coma, papilledema, or focal neurological findings. Should imaging be performed with the inherent delay, the recommendation is to obtain blood cultures and initiate antibiotic therapy before CT and LP. (1)

Emergency Department Care

Recognition and prompt treatment are key. In meningitis, at times this is quite straightforward but at times it is not. The patient with altered mental status may not give a meaningful history and fine examination for nuchal rigidity or other abnormalities may be difficult. Fever is not initially present in some cases.

When the diagnosis of acute bacterial meningitis is suspected, antibiotics should be promptly administered and not be delayed for imaging or procedures (see discussion above). Initial antibiotic treatment is largely based on risk factors. In the absence of recent trauma or neurosurgical procedures, known contacts, or a pathognomonic rash, treatment will be empiric based mainly on the patient's age. In general, this means treatment with a third generation cephalosporin (ceftriaxone or cefotaxime) and vancomycin. Additionally, ampicillin is often recommended for children less than three months of age or for adults over 50.

A recent prospective study in adults with bacterial meningitis has strengthened the argument for administering steroids early in treatment; in the study protocol steroids were administered 15-20 minutes before antibiotics. (9) The accompanying editorial recommends steroid administration either just before or at the time of steroid administration. (10) There is the concern that steroids, through limiting meningeal inflammation, may interfere with penetration of vancomycin into the CNS but this is not thought to be of clinical significance.

It is important to remember to treat close contacts of patients with meningitis from *Neisseria meningitidis*; rifampin (pediatric dose 10 mg/kg; adult dose 600mg) PO q12h X 4 doses or ciprofloxacin (adults 500 mg PO once) are the recommended medications.

Consultations and Admission

In general, ICU admission is recommended until patient condition improves because of the potential for early complications such as seizures or stroke symptoms. Typically consultation with infectious disease services is recommended when meningitis is discovered. Meningitis may be a reportable illness to local public health authorities though often this is done by laboratory personnel.

References

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5. Scheld WM, et al: Pathophysiology of bacterial meningitis: mechanism(s) of neuronal injury. *J Infect Dis* 2002; 186 Suppl 2: S225-33.
6. Attia J, et al: The rational clinical examination. Does this adult patient have acute meningitis? *JAMA* 1999; 282(2): 175-81.
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8. Uchihara T, Tsukagoshi H: Jolt accentuation of headache: the most sensitive sign of CSF pleocytosis. *Headache* 1991; 31(3): 167-71.
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10. de Gans J, van de Beek D: Dexamethasone in adults with bacterial meningitis. *N Engl J Med* 2002; 347(20): 1549-56.
11. Tunkel AR, Scheld, WM: Corticosteroids for everyone with meningitis? *N Engl J Med* 2002; 347(20): 1613-5.

Patient Outcome

Diagnosis: Acute bacterial meningitis from *S. pneumoniae* with predisposing condition of post-surgical encephalocele.

The patient received ceftriaxone 2 grams intravenously prior to neuroimaging. CT showed sinus disease with diffuse mucosal thickening but no other abnormalities. Following the lumbar puncture that showed cloudy fluid evident to visual inspection, the patient additionally received vancomycin and acyclovir.

Lumbar puncture cell count showed 16,000 WBC, 99% segmented forms. CSF glucose was less than 10; protein was 522. Gram stain showed white cells but no bacteria. Lactic acid was 10.9. Peripheral WBC 18,500 and routine chemistry was normal.

The patient was admitted to the ICU for one day; mental status improved but headache persisted. Blood cultures were all positive for *Streptococcus pneumoniae*, sensitive to penicillin. Other medications were discontinued except for pain medications. The patient was discharged home where she completed a two-week course of antibiotics.

The patient returned to work three weeks after admission without sequelae. At ENT consultation one month later for persistent sinusitis, endoscopic examination and further imaging established the existence of a right encephalocele, a complication of earlier elective sinus surgery (FESS). This was electively repaired.

Annotated Bibliography

1. Attia, J, Hatala, R, Cook, DJ and Wong, JG. "The rational clinical examination. Does this adult patient have acute meningitis?" *JAMA* (1999);282(2): 175-81.

From the JAMA rational clinical examination series; reviews accuracy and precision of clinical examination in the diagnosis of adult meningitis. The classic triad of meningitis-fever, stiff neck, and altered mental status-is present in less than 2/3 of patients with meningitis. Many of the traditional signs of meningitis-Kernig's and Brudzinski signs-though specific for meningeal irritation appear to be lacking in sensitivity. Their review suggests that an uncommonly used maneuver-jolt accentuation of headache-is sensitive for meningitis and may aid in the decision to proceed to lumbar puncture inpatients at risk for meningitis.

2. de Gans, J and van de Beek, D. "Dexamethasone in adults with bacterial meningitis." *N Engl J Med* (2002);347(20): 1549-56.

Prospective, randomized double-blind multicenter trial of dexamethasone use in adults suggest conclusive benefit for adjunctive use of steroids. Mortality and unfavorable outcomes were fewer in the treated group. Protocol called for administration of dexamethasone 10 mg 15-20 minutes before administration of first dose of antibiotics, usually amoxicillin (low penicillin resistance in Europe), with steroids continued every six hours for four days.

3. Kastenbauer, S and Pfister, HW. "Pneumococcal meningitis in adults: Spectrum of complications and prognostic factors in a series of 87 cases." *Brain* (2003);126(Pt 5): 1015-25.

German study describing 87 consecutive cases of adult pneumococcal meningitis over a 18-year period. Mortality rate was 24%. 30% of patients had cerebrovascular complications. Cerebral edema was diagnosed in 29% and hydrocephalus in 16%. Poor prognostic factors included a low GCS on admission, bacteremia, and pneumonia. Lower CSF leukocyte counts were associated with adverse outcomes.

4. Lipton, JD and Schafermeyer, RW. "Evolving concepts in pediatric bacterial meningitis-Part I: Pathophysiology and diagnosis. Part II: Current management and therapeutic research." *Ann Emerg Med* (1993);22(10): 1602-15; 1616-29.

Exhaustive review in emergency medicine literature of epidemiology, pathogenesis, clinical presentations, and therapy of pediatric bacterial meningitis. Still valuable despite age.

5. Quagliarello, VJ and Scheld, WM. "Treatment of bacterial meningitis." *N Engl J Med* (1997);336(10): 708-16.

Review of treatment for bacterial meningitis by thought leaders in the field. Now 6 years old but still recommended. Included in the discussion are statements that antibiotic therapy one or two hours before lumbar puncture will not decrease the diagnostic sensitivity if CSF antigen testing and blood cultures are performed. Consensus opinion has changed on steroid use and empiric treatment with vancomycin since the writing of this article.

6. Scheld, WM, Koedel, U, Nathan, B and Pfister, HW. "Pathophysiology of bacterial meningitis: mechanism(s) of neuronal injury." *J Infect Dis* (2002);186 Suppl 2: S225-33.

Review of changing epidemiology of acute bacterial meningitis and basic pathophysiologic mechanisms of CNS injury. Describes a vicious cycle of pathophysiologic alterations in acute bacterial meningitis starting at the cellular level with final pathways of increased intracranial pressure and decreased cerebral perfusion pressure or herniation.

7. Talan, DA, Guterman, JJ, Overturf, GD, Singer, C, Hoffman, JR and Lambert, B.
"Analysis of emergency department management of suspected bacterial meningitis." *Ann Emerg Med* (1989);18(8): 856-62.

Landmark study showing that the often-recommended "antibiotics within 30 minutes" statement was not in fact what was happening in the ED. This retrospective review noted that long-delays to antibiotic administration in the ED were frequently encountered and that many of these delays could potentially be shortened or eliminated.

Questions

1. **Which of the following are risk factors for meningitis in adults?**
 - a. Diabetes mellitus
 - b. Otitis media
 - c. Sinusitis
 - d. Alcoholism
 - e. All of the above

2. **Which of the following is the best test for meningeal irritation and predicting the need for lumbar puncture?**
 - a. Nuchal rigidity
 - b. Kernig's sign
 - c. Brudzinski's sign
 - d. None are sensitive enough to base clinical decisions on solely presence or absence
 - e. All are equivalent

3. **The most common organism in adult meningitis in the US is which of the following?**
 - a. E. coli
 - b. S. pneumoniae
 - c. H. influenza
 - d. Listeria monocytogenes
 - e. Neisseria species

4. **Initial antibiotic therapy for acute bacterial meningitis in adults less than 50 years of age ...?**
 - a. Should include vancomycin as well as a third generation cephalosporin in view of increasing penicillin resistance of *S. pneumoniae*
 - b. Should be guided by Gram stain
 - c. Should include ampicillin
 - d. Should never be administered before CSF culture is obtained
 - e. Should include acyclovir

5. **Current innovations in treatment of acute bacterial meningitis are mainly directed along the lines of which of the following?**
 - a. New broad spectrum antibiotics
 - b. Antibiotics for penicillin resistant organisms
 - c. Cerebral neuroprotective agents
 - d. Anti-inflammatory agents
 - e. Rapidly absorbed oral agents

6. **Steroid administration in cases of acute bacterial meningitis...?**
 - a. Is unproven
 - b. Is effective only in preventing hearing loss in infants
 - c. Dexamethasone 10 mg at time of antibiotic administration in adults is recommended
 - d. Dexamethasone 10 mg before antibiotic administration in adults is recommended
 - e. Both c and d are acceptable

Answers

1. Answer e.

Diabetes mellitus, sinusitis, otitis media, alcoholism as well as pneumonia are all risk factors for bacterial meningitis in adults.

2. Answer d.

None of these bedside tests are alone sensitive enough to exclude possibility of meningitis.

3. Answer b.

S. pneumoniae continues to be the most common agent in adults causing acute meningitis.

4. Answer a.

Vancomycin as well as a third generation cephalosporin should be initial empiric therapy in view of increasing penicillin resistance of *S. pneumoniae*.

5. Answer d.

Most current research is directed not toward more effective antibiotic development but to agents such as steroids that may interrupt the inflammatory cascade with resultant vasculitis and cerebral edema.

6. Answer e.

Recent recommendation calls for administration of 10 mg dexamethasone immediately before or at time of antibiotic administration in adults.