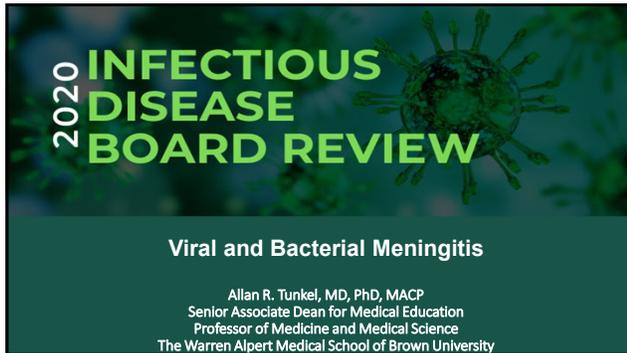


23 –Viral and Bacterial Meningitis

Speaker: Allan Tunkel, MD



2020 INFECTIOUS DISEASE BOARD REVIEW

Viral and Bacterial Meningitis

Allan R. Tunkel, MD, PhD, MACP
Senior Associate Dean for Medical Education
Professor of Medicine and Medical Science
The Warren Alpert Medical School of Brown University

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

CASE #1

- 38-year-old woman presents with a 2-day history of fever, headache and stiff neck; similar episodes have occurred every 3-4 months over several years, with spontaneous abatement after 4-5 days
- She is sexually active only with her husband of 8 years, and has 2 children at home (ages 2 and 5 years)
- On exam, T 99.8°F and other vital signs are normal; she has evidence of meningismus, but is alert and oriented and with no focal findings
- Laboratory studies are normal
- CSF analysis reveals a WBC of 70/mm³ (100% lymphs), glucose of 60 mg/dL, and protein of 100 mg/dL; Gram stain negative

QUESTION #1

Which of the following is the most likely etiology of this patient's meningitis?

- A. Coxsackie A virus
- B. Coxsackie B virus
- C. Human immunodeficiency virus
- D. Herpes simplex virus type 2
- E. Human herpesvirus 6

VIRAL MENINGITIS Major Etiologies

- Enteroviruses
- Mumps virus
- Herpesviruses
- Lymphocytic choriomeningitis virus
- Others
 - Arboviruses
 - Human immunodeficiency virus
 - Adenovirus
 - Parainfluenza virus types 2 and 3

Cerebrospinal Fluid Findings in Viral Meningitis

CSF Parameter	Viral
Opening pressure	≤ 250 mm H ₂ O
WBC count	50-1000/mm ³
WBC differential	Lymphocytes
Glucose	>45 mg/dL
CSF: serum glucose	>0.6
Protein	<200 mg/dL
Gram stain	Negative

23 –Viral and Bacterial Meningitis

Speaker: Allan Tunkel, MD

Enteroviruses

- Leading cause of “aseptic” meningitis syndrome
- Accounts for 85-95% of cases with identified etiology
- 30,000-75,000 cases annually in US (low estimate)
- Summer/fall seasonality; outbreaks reported
- Fecal-oral spread
- ~100 serotypes; 14 account for 80% of isolates
- CEMA (chronic enteroviral meningoencephalitis in agammaglobulinemia)
- Rituximab

Enteroviruses

- Clinical clues
 - Time of year
 - Outbreak in community
 - Other recognizable enteroviral syndromes
- Specific etiologies
 - Scattered maculopapular rash: echovirus 9
 - Herpangina: coxsackievirus A
 - Pericarditis/pleuritis: coxsackievirus B
 - Rhombencephalitis: enterovirus 71

Enteroviruses

- Symptoms and signs
 - Fever, headache, nuchal rigidity (>50%), photophobia
- Diagnosis
 - Neutrophils may predominate in CSF early (up to 48 hrs)
 - CSF virus isolation (sensitivity 65-75%)
 - Virus isolation from throat or rectum
 - PCR (sensitivity 86-100%; specificity 92-100%)
- Therapy
 - Supportive

Mumps Virus

- Common in unimmunized populations
- Occurs in 10-30% of mumps patients overall
- Peak in children 5-9 years of age; males>females
- Can occur in patients without parotitis; 40-50% have no evidence of salivary gland enlargement
- Symptoms and sign usually follow onset of parotitis (if present) by ~5 days
- Diagnosis
 - Serology
 - CSF RT-PCR
 - CSF culture (sensitivity 30-50%)

Herpes Simplex Virus

- Self-limited syndrome
- Most commonly with primary HSV-2 genital infection
 - 36% of women
 - 13% of men
- Less likely with recurrence of genital herpes
- Recurrent benign lymphocytic meningitis (Mollaret)
 - Most caused by HSV-2
 - Few or at least 10 episodes lasting 2-5 days followed by spontaneous recovery
 - Fever, headache, photophobia, meningismus

Herpes Simplex Virus

- Diagnosis
 - Lymphocytic pleocytosis (<500 cells/mm³); normal glucose, elevated protein
 - CSF PCR
- Therapy
 - Usually self-limited; unclear if antiviral therapy alters course of mild meningitis
 - Suppressive therapy (valacyclovir) not indicated for recurrent disease; associated with a higher frequency of meningitis after cessation of active drug

23 -Viral and Bacterial Meningitis

Speaker: Allan Tunkel, MD

Lymphocytic Choriomeningitis Virus

- Now rarely reported as an etiologic agent
- Transmitted to humans by contact with rodents (hamsters, rats, mice) or their excreta
- Risk groups
 - Laboratory workers
 - Pet owners
 - Persons living in impoverished or unhygienic places
 - Rodent breeding factory
- No evidence of human-to-human transmission

CASE #2

- 60-year-old man with chronic kidney disease immigrated from Brazil to the US and underwent a cadaveric renal transplant
- Prior to transplant, he had episodes of recurrent epigastric pain. At the time, his WBC was $6,500/\text{mm}^3$ with 15% eosinophils
- After transplant, he received immunosuppressive therapy

CASE #2

- Presented 1 month later with headache, meningismus and altered mental status, and a temperature of $T 39^\circ\text{C}$
- Lumbar puncture had WBC $2500/\text{mm}^3$ (98% neutrophils), glucose 20 mg/dL, and protein 450 mg/dL
- Placed on empiric antimicrobial therapy with vancomycin, ampicillin, and ceftriaxone
- Cultures of blood and CSF grew *Escherichia coli*

Question #2

Which of the following diagnostic tests would most likely establish the pathogenesis of *E. coli* meningitis in this patient?

- A. MRI of the head and sinuses
- B. Right upper quadrant ultrasound
- C. Serial stool examinations
- D. Cisternography
- E. Colonoscopy

EPIDEMIOLOGIC FEATURES OF PNEUMOCOCCAL MENINGITIS

- Most common etiologic agent in US (58% of cases)
- Mortality of 18-26%
- Associated with other suppurative foci of infection
 - Pneumonia (25%)
 - Otitis media or mastoiditis (30%)
 - Sinusitis (10-15%)
 - Endocarditis (<5%)
 - Head trauma with CSF leak (10%)

EPIDEMIOLOGIC FEATURES OF MENINGOCOCCAL MENINGITIS

- Children and young adults; mortality 3-13%
- Serogroups A, B, C, W, and Y
- Serogroup B disease in recent outbreaks (Princeton, UC-Santa Barbara, Providence College)
- Predisposition in those with congenital deficiencies in terminal complement components (C5-C8, and perhaps C9) and properdin deficiencies
- Increased risk: MSM, HIV infection, eculizumab

23 –Viral and Bacterial Meningitis

Speaker: Allan Tunkel, MD

EPIDEMIOLOGIC FEATURES OF GROUP B STREPTOCOCCAL MENINGITIS

- Important etiologic agent in neonates; mortality 7-27%
- Early-onset septicemia associated with prematurity, premature rupture of membranes, low birth weight
- Late onset meningitis (> 7 days after birth)
- Disease in adults associated with the following:

Diabetes mellitus	Parturient women
Cardiac, hepatic, renal disease	Malignancy
Collagen-vascular disorders	Alcoholism
HIV infection	Corticosteroid use

EPIDEMIOLOGIC FEATURES OF LISTERIA MENINGITIS

- Rare etiology in US (2-8%); mortality 15-29%
- Outbreaks associated with consumption of contaminated cole slaw, raw vegetables, milk, cheese, processed meats, cantaloupe, diced celery, ice cream, hog head cheese
- Common in neonates
- Low in young, previously healthy persons (4-10%)
- Disease in adults associated with:

Elderly	Alcoholism
Malignancy	Immune suppression
Diabetes mellitus	Hepatic and renal disease
Iron overload	Collagen-vascular disorders
HIV infection	Biologic therapies

EPIDEMIOLOGIC FEATURES OF AEROBIC GRAM-NEGATIVE BACILLARY MENINGITIS

- *Klebsiella* species, *Escherichia coli*, *Serratia marcescens*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Salmonella* species
- Isolated from CSF of patients following head trauma or neurosurgical procedures
- Cause meningitis in neonates, the elderly, immunocompromised patients, and in patients with gram-negative septicemia
- Associated with disseminated strongyloidiasis in the hyperinfection syndrome

EPIDEMIOLOGIC FEATURES OF HAEMOPHILUS INFLUENZAE MENINGITIS

- Causes 7% of cases in US; mortality 3-7%
- Capsular type b strains were previously in >90% of serious infections; children <6 years of age (peak 6-12 months)
- Concurrent pharyngitis or otitis media in >50% of cases
- Disease in persons >6 years of age associated with:

Sinusitis or otitis media	Pneumonia
Sickle cell disease	Splenectomy
Diabetes mellitus	Immune deficiency
Head trauma with CSF leak	Alcoholism

OTHER BACTERIAL ETIOLOGIES OF MENINGITIS

Bacterial Etiology	Risk Factors
<i>Staphylococcus aureus</i>	Neurosurgery, trauma, diabetes mellitus, alcoholism, hemodialysis, injection drug use, malignancy
<i>Staphylococcus epidermidis</i>	CSF shunts and drains
Diphtheroids (e.g., <i>Cutibacterium acnes</i>)	CSF shunts and drains
Anaerobes	Contiguous foci in head and neck
<i>Streptococcus salivarius</i>	Spinal anesthesia, myelogram
<i>Streptococcus suis</i>	Vietnam, eating undercooked pig blood or pig intestine, pig exposure

INCIDENCE OF BACTERIAL MENINGITIS (UNITED STATES)

Organism	Incidence (cases per 100,000)		
	1986	1995	2006-2007
<i>H. influenzae</i>	2.9	0.2	0.08
<i>S. pneumoniae</i>	1.1	1.1	0.81
<i>N. meningitidis</i>	0.9	0.6	0.19
Group B streptococcus	0.4	0.3	0.25
<i>L. monocytogenes</i>	0.2	0.2	0.05

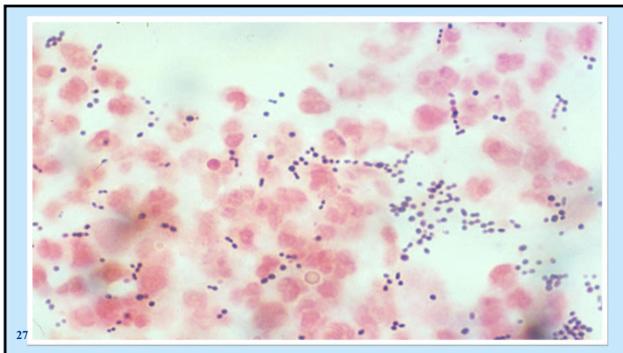
23 –Viral and Bacterial Meningitis

Speaker: Allan Tunkel, MD

CEREBROSPINAL FLUID FINDINGS IN BACTERIAL VERSUS VIRAL MENINGITIS		
CSF Parameter	Bacterial	Viral
Opening pressure	200-500 mm H ₂ O	≤ 250 mm H ₂ O
WBC count	1000-5000/mm ³	50-1000/mm ³
WBC differential	Neutrophils	Lymphocytes
Glucose	<40 mg/dL	>45 mg/dL
CSF: serum glucose	≤ 0.4	>0.6
Protein	100-500 mg/dL	<200 mg/dL
Gram stain	(+) in 60-90%	Negative

CASE #3

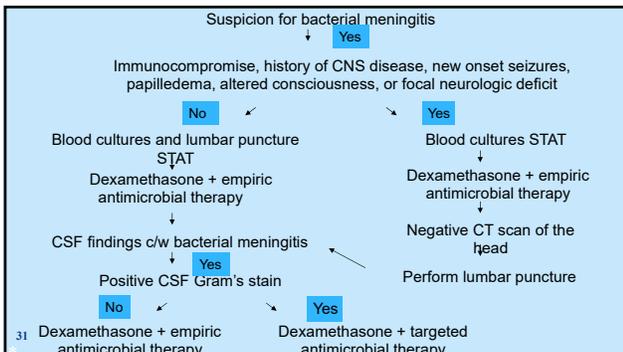
- A 35-year-old woman presents to the hospital with a 2-day history of fever, chills, headache, and confusion. She has a history of diabetes mellitus and recently delivered a healthy child
- T 40.5°C, P 140, RR 32, BP 90/60 mmHg
- Obtunded, stiff neck
- WBC 30,000/mm³ (40% bands), platelets 20,000/mm³
- Lumbar puncture revealed an opening pressure of 280 mm H₂O, WBC 2500/mm³ (99% segs), glucose 20 mg/dL, and protein 400 mg/dL



Question #3

In addition to adjunctive dexamethasone, which of the following regimens should be initiated?

- Ampicillin + gentamicin
- Ampicillin + ceftriaxone
- Vancomycin + ampicillin
- Vancomycin + ceftriaxone
- Vancomycin + trimethoprim-sulfamethoxazole



EMPIRIC ANTIMICROBIAL THERAPY OF PURULENT MENINGITIS

Age	Antimicrobial Therapy
<1 month	Ampicillin + cefotaxime; ampicillin + cefepime
1-23 months	Vancomycin + a third-generation cephalosporin ^a
2-50 years	Vancomycin + a third-generation cephalosporin ^{a,b,c}
Older than 50 years	Vancomycin + ampicillin + a third-generation cephalosporin ^a

^aceftriaxone or cefotaxime
^bsome experts would add rifampin if dexamethasone is also given
^cadd ampicillin if Listeria is suspected

23 –Viral and Bacterial Meningitis

Speaker: Allan Tunkel, MD

EMPIRIC ANTIMICROBIAL THERAPY OF PURULENT MENINGITIS	
Predisposing Condition	Antimicrobial Therapy
Immunocompromise	Vancomycin + ampicillin + either meropenem or cefepime
Basilar skull fracture	Vancomycin + a third generation cephalosporin ^a
Head trauma or after neurosurgery	Vancomycin + either ceftazidime or cefepime or meropenem
Cerebrospinal fluid shunt or drain	Vancomycin + either ceftazidime or cefepime or meropenem

^aceftriaxone or cefotaxime

TARGETED ANTIMICROBIAL THERAPY IN BACTERIAL MENINGITIS	
Microorganism	Antimicrobial Therapy
<i>S. pneumoniae</i>	Vancomycin + a third-generation cephalosporin ^{a,b}
<i>N. meningitidis</i>	Third-generation cephalosporin ^a
<i>H. influenzae</i>	Third-generation cephalosporin ^a
<i>L. monocytogenes</i>	Ampicillin or penicillin G ^c

^aceftriaxone or cefotaxime
^baddition of rifampin may be considered, especially if dexamethasone given
^caddition of an aminoglycoside may be considered

ANTIMICROBIAL THERAPY IN BACTERIAL MENINGITIS	
Organism	Antimicrobial Therapy
<i>Streptococcus pneumoniae</i>	
PCN MIC <0.06 µg/mL	Penicillin G or ampicillin
PCN MIC ≥0.12 µg/mL	
CTX ^a MIC <1.0 µg/mL	Third-generation cephalosporin ^a
CTX ^a MIC ≥1.0 µg/mL	Vancomycin + a third-generation cephalosporin ^{a,b}

^aceftriaxone or cefotaxime
^bconsider addition of rifampin if ceftriaxone MIC >4 µg/mL

ANTIMICROBIAL THERAPY IN BACTERIAL MENINGITIS	
Organism	Antimicrobial Therapy
<i>Neisseria meningitidis</i>	
PCN MIC <0.1 µg/mL	Penicillin G or ampicillin
PCN MIC 0.1-1.0 µg/mL	Third-generation cephalosporin ^a
<i>Haemophilus influenzae</i>	
β-lactamase-negative	Ampicillin
β-lactamase-positive	Third-generation cephalosporin ^a

^aceftriaxone or cefotaxime

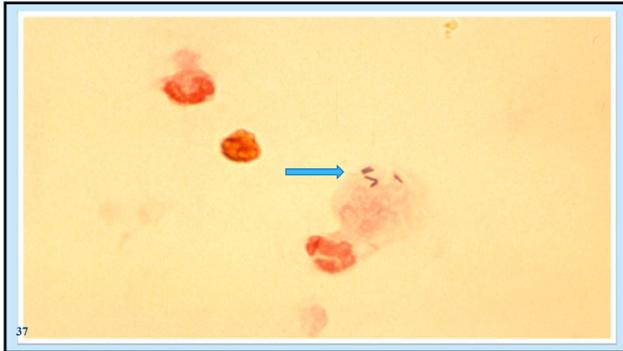
ANTIMICROBIAL THERAPY IN BACTERIAL MENINGITIS	
Organism	Antimicrobial Therapy
<i>Pseudomonas aeruginosa</i>	Ceftazidime or cefepime or meropenem
<i>Acinetobacter baumannii</i>	Meropenem or colistin (formulated as colistimethate sodium) ^a or polymyxin B ^a
<i>Streptococcus agalactiae</i>	Ampicillin or penicillin G ^b
<i>Listeria monocytogenes</i>	Ampicillin or penicillin G ^b
<i>Staphylococcus aureus</i>	
MSSA	Nafcillin or oxacillin
MRSA	Vancomycin

^amight also need to be administered by intraventricular or intrathecal routes
^baddition of an aminoglycoside should be considered

- ### CASE #4
- 60-year-old male with chronic lymphocytic leukemia presented with fever, headache, ataxia, and altered mental status. Recently traveled to an outdoor family picnic in rural Virginia. He is allergic to penicillin (anaphylaxis)
 - T 102°F, P 120, RR 24, BP 100/60 mmHg
 - He was obtunded and had nuchal rigidity
 - WBC was 25,000/mm³ (30% bands)
 - LP revealed a WBC 1500/mm³ (50 neutrophils, 50% lymphocytes), glucose 30 mg/dL, and protein 200 mg/dL

23 -Viral and Bacterial Meningitis

Speaker: Allan Tunkel, MD



Question #4

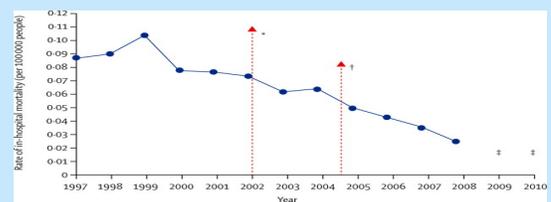
Which of the following antimicrobial regimens should be initiated?

- A. Vancomycin
- B. Trimethoprim-sulfamethoxazole
- C. Chloramphenicol
- D. Moxifloxacin
- E. Daptomycin

ADJUNCTIVE DEXAMETHASONE IN BACTERIAL MENINGITIS

- Attenuates subarachnoid space inflammatory response resulting from antimicrobial-induced lysis
- Recommended for infants and children with *Haemophilus influenzae* type b meningitis and considered for pneumococcal meningitis in childhood, given before or with parenteral antimicrobial therapy
- Recommended in adults with pneumococcal meningitis
- Administer at 0.15 mg/kg IV every 6 hours for 4 days in adults concomitant with or just before first antimicrobial dose

IN-HOSPITAL MORTALITY FOR PNEUMOCOCCAL MENINGITIS



Castelblanco et al. Lancet ID 2014;14:813