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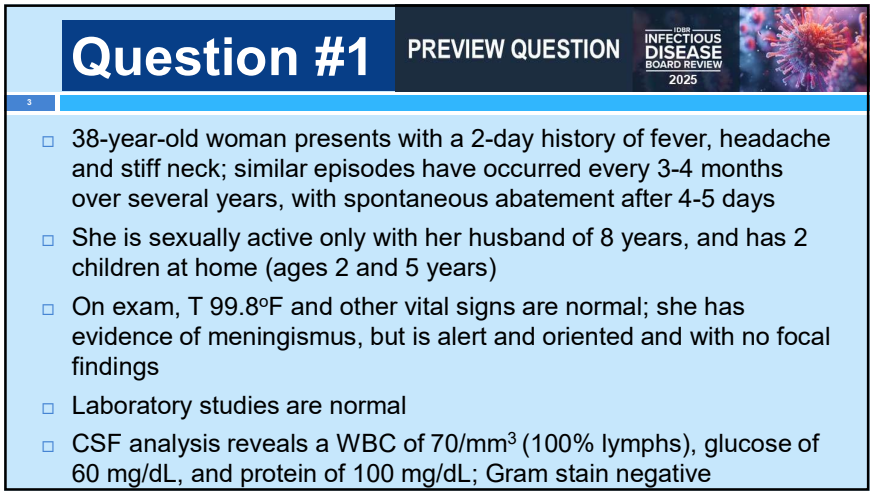


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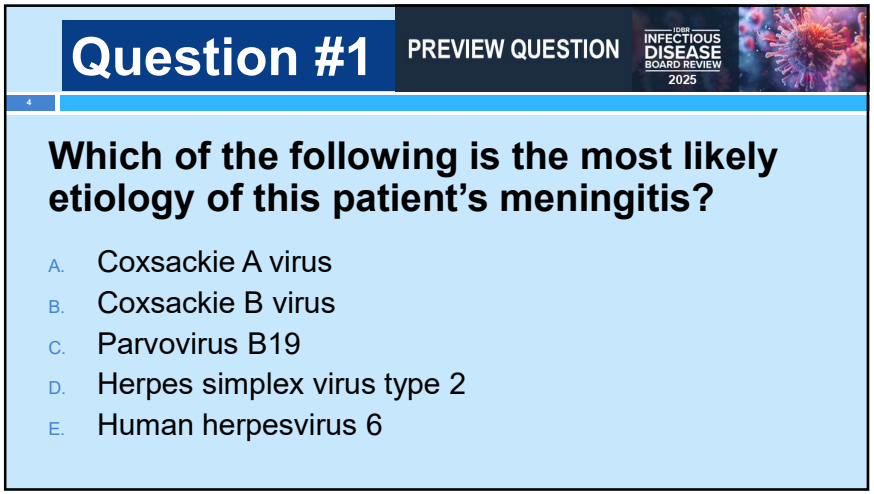


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**43 Bacterial and Viral Meningitis**
*Speaker: Allan Tunkel, MD, PhD, MACP*

## Viral Meningitis
### Major Etiologies

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

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## Cerebrospinal Fluid (CSF) Findings in Viral Meningitis

6

| CSF Parameter | CSF Findings |
|---|---|
| Opening pressure | ≤ 250 mm $H_2O$ |
| 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 |

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## Enteroviruses

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- 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

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## Enteroviruses

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- 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

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## Enteroviruses

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- 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

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## Mumps Virus

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- 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 signs usually follow onset of parotitis (if present) by ~5 days
- Diagnosis
  - Serology
  - CSF RT-PCR
  - CSF culture (sensitivity 30-50%)

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## Herpes Simplex Virus

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- 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

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## Herpes Simplex Virus

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- Diagnosis
  - Lymphocytic pleocytosis (<500 cells/mm$^3$); normal glucose, elevated protein
  - CSF PCR
- Therapy
  - Usually self-limited; unclear if antiviral therapy alters course of mild meningitis, but usually recommended
  - Suppressive therapy (valacyclovir) not indicated for recurrent disease; associated with a higher frequency of meningitis after cessation of active drug

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## Lymphocytic Choriomeningitis Virus

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- Now rarely reported as an etiologic agent
- Transmitted to humans by contact with rodents (hamsters, rats, mice) or their excreta
- As estimated 5% of house mice in the US are infected; infection more common in winter when mice are indoors
- Risk groups
  - Laboratory workers
  - Pet owners
  - Persons living in impoverished or unhygienic places
  - Rodent breeding factory
- No evidence of human-to-human transmission

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## Question #2

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- 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/mm$^3$ with 15% eosinophils
- After transplant, he received immunosuppressive therapy

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## Question #2

15

- Presented 1 month later with headache, meningismus and altered mental status, and a temperature of T 39$^o$C
- Lumbar puncture had WBC 2500/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*

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## Question #2

16

**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

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## Epidemiologic Features of Pneumococcal Meningitis

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- 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%)

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## Epidemiologic Features of Meningococcal Meningitis

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- Children and young adults; mortality 3-13%
- Serogroups A, B, C, W, and Y
- Serogroup B disease in recent outbreaks
- Predisposition in those with congenital deficiencies in terminal complement components (C5-C8, and perhaps C9) and properdin deficiencies
- Increased risk: MSM, HIV infection, use of complement inhibitors that block C5 (eculizumab, ravulizumab), microbiologists exposed to isolates, travel to epidemic or hyperendemic areas, outbreak-related, college students

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## Epidemiologic Features of Group B Streptococcal Meningitis

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- 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 |

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## Epidemiologic Features of *Listeria* Meningitis

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

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## Epidemiologic Features of Aerobic Gram-negative Bacillary Meningitis

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

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## Epidemiologic Features of *Haemophilus Influenzae* Meningitis

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- 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 |

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## Other Bacterial Etiologies of Meningitis

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

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## Incidence of Bacterial Meningitis (United States)

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

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## Cerebrospinal Fluid Findings in Bacterial Versus Viral Meningitis

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| CSF Parameter | Bacterial | Viral |
|---|---|---|
| Opening pressure | 200-500 mm $H_2O$ | ≤ 250 mm $H_2O$ |
| 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 |

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## Meningitis/Encephalitis Panel

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| Bacteria | Viruses | Fungi |
|---|---|---|
| *Escherichia coli* K1 | Cytomegalovirus | *Cryptococcus neoformans/gatti* |
| *Haemophilus influenzae* | Enterovirus | |
| *Listeria monocytogenes* | Herpes simplex virus 1 | |
| *Neisseria meningitidis* | Herpes simplex virus 2 | |
| *Streptococcus agalactiae* | Human herpesvirus 6 | |
| *Streptococcus pneumoniae* | Human parechovirus | |
| | Varicella zoster virus | |

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## Question #3

27

- A 25-year-old man presents to the hospital with a 2-day history of fever, chills, headache, and mild confusion. He has paroxysmal nocturnal hemoglobinuria and is currently on therapy with ravulizumab; he also takes oral penicillin V daily. Prior to starting ravulizumab; he received the quadrivalent (ACWY) meningococcal conjugate vaccine and the serogroup B meningococcal vaccine.
- T 40.5°C, P 120, RR 28, BP 90/60 mmHg; obtunded, stiff neck
- WBC 30,000/$mm^3$ (40% bands), platelets 40,000/$mm^3$
- Lumbar puncture revealed an opening pressure of 300 mm $H_2O$, WBC 1500/$mm^3$ (99% segs), glucose 20 mg/dL, and protein 300 mg/dL

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## Question #3

28

**Which of the following empiric antimicrobial regimens should be initiated?**

A. Penicillin G
B. Ceftriaxone
C. Vancomycin + ampicillin
D. Vancomycin + ceftriaxone

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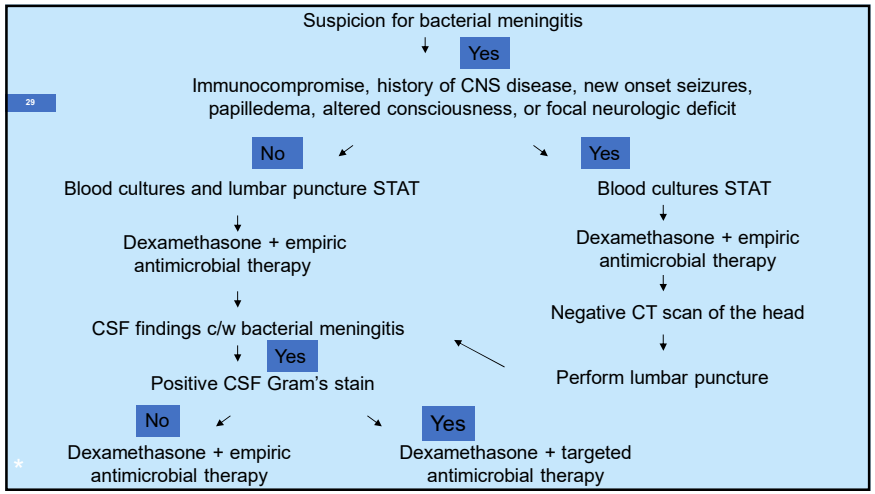


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## Empiric Antimicrobial Therapy of Purulent Meningitis

| Age | Antimicrobial Therapy |
|---|---|
| <1 month | Ampicillin + gentamicin + either cefotaxime (if available) or 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] |

[a]ceftriaxone or cefotaxime
[b]some experts would add rifampin if dexamethasone is also given
[c]add ampicillin if Listeria is suspected

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## 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 |

[a]ceftriaxone or cefotaxime

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## Targeted Antimicrobial Therapy in Bacterial Meningitis

| Microorganism | Antimicrobial Therapy |
|---|---|
| *S. pneumoniae* | Vancomycin + a third-generation cephalosporin[a,b] |
| *N. meningitidis* | Third-generation cephalosporin[a] |
| *H. influenzae* | Third-generation cephalosporin[a] |
| *L. monocytogenes* | Ampicillin or penicillin G[c] |

[a]ceftriaxone or cefotaxime
[b]addition of rifampin may be considered, especially if dexamethasone given
[c]addition of an aminoglycoside may be considered

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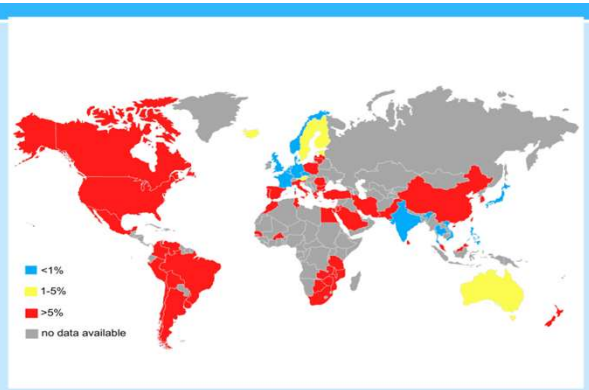
## Pneumococcal Susceptibility to Penicillin

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## Pneumococcal Susceptibility to Penicillin

| | Minimal Inhibitory Concentration |
|---|---|
| Susceptible | ≤0.06 mg/mL |
| Resistant | ≥0.12 mg/mL |

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## Antimicrobial Therapy in Bacterial Meningitis

| Organism | Antimicrobial Therapy |
|---|---|
| *Streptococcus pneumoniae* | |
| PCN MIC ≤0.06 mg/mL | Penicillin G or ampicillin |
| PCN MIC ≥0.12 mg/mL | |
| CTX[a] MIC <1.0 mg/mL | Third-generation cephalosporin[a] |
| CTX[a] MIC ≥1.0 mg/mL | Vancomycin + a third-generation cephalosporin[a,b] |

[a]ceftriaxone or cefotaxime
[b]consider addition of rifampin if ceftriaxone MIC ≥4 mg/mL

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## Antimicrobial Therapy in Bacterial Meningitis

| Organism | Antimicrobial Therapy |
|---|---|
| *Neisseria meningitidis* | |
| PCN MIC <0.1 mg/mL | Penicillin G or ampicillin |
| PCN MIC 0.1-1.0 mg/mL | Third-generation cephalosporin[a] |
| *Haemophilus influenzae* | |
| b-lactamase-negative | Ampicillin |
| b-lactamase-positive | Third-generation cephalosporin[a] |

[a]ceftriaxone or cefotaxime

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## Antimicrobial Therapy in Bacterial Meningitis

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| Organism | Antimicrobial Therapy |
|---|---|
| *Pseudomonas aeruginosa* | Ceftazidime or cefepime or meropenem |
| *Acinetobacter baumannii* | Meropenem or colistin (formulated as colistimethate sodium)[a] or polymyxin B[a] |
| *Streptococcus agalactiae* | Ampicillin or penicillin G |
| *Listeria monocytogenes* | Ampicillin or penicillin G[b] |
| *Staphylococcus aureus* | |
| MSSA | Nafcillin or oxacillin |
| MRSA | Vancomycin |

[a]also administered by intraventricular or intrathecal routes
[b]addition of an aminoglycoside should be considered

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## Question #4

38

- 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/mm$^3$ (30% bands)
- LP revealed a WBC 1500/mm$^3$ (50 neutrophils, 50% lymphocytes), glucose 30 mg/dL, and protein 200 mg/dL

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## Question #4

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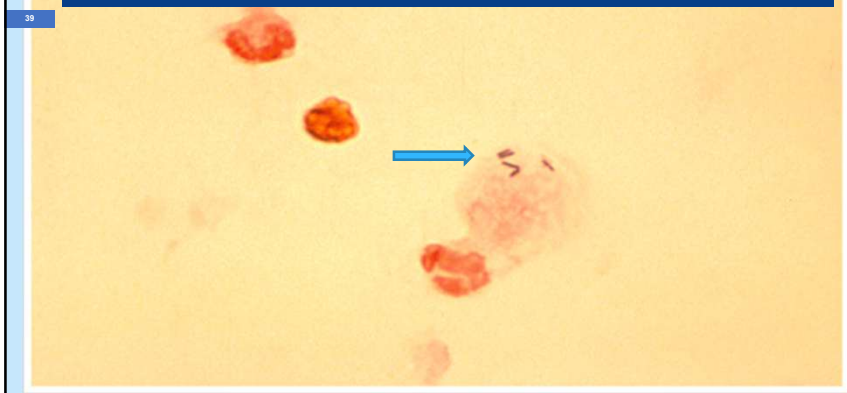

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## Question #4

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**Which of the following antimicrobial regimens should be initiated?**

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

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## Adjunctive Dexamethasone in Bacterial Meningitis

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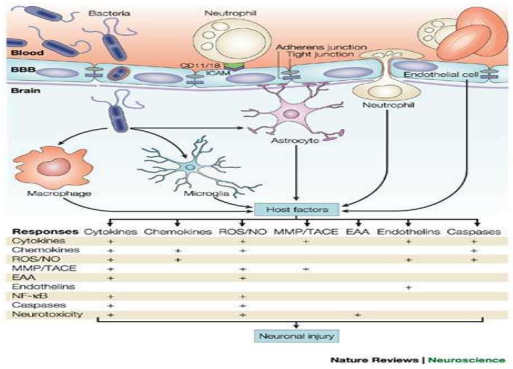


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## Adjunctive Dexamethasone in Bacterial Meningitis

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- 301 adults with bacterial meningitis ≥17 years of age
- Randomized, double blind, placebo-controlled
- Dexamethasone (0.15 mg mg/kg q 6 hr for 4 days) given 15-20 minutes before first antimicrobial dose
- All patients: reduction in unfavorable outcome (15 vs 25% P=0.03) and mortality (7 vs 15%; P=0.04)
- Pneumococcal meningitis: reduction in unfavorable outcome (26 vs 52%; P=0.006) and mortality (14 vs 34%; P=0.02)

de Gans and van de Beek. N Engl J Med 2002;347:1549

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## Adjunctive Dexamethasone in Bacterial Meningitis

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- 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 bacterial meningitis
- Administer at 0.15 mg/kg IV every 6 hours for 4 days in adults concomitant with or just before first antimicrobial dose; European guidelines endorse use up to 4 hours after antimicrobial therapy

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## In-Hospital Mortality for Pneumococcal Meningitis

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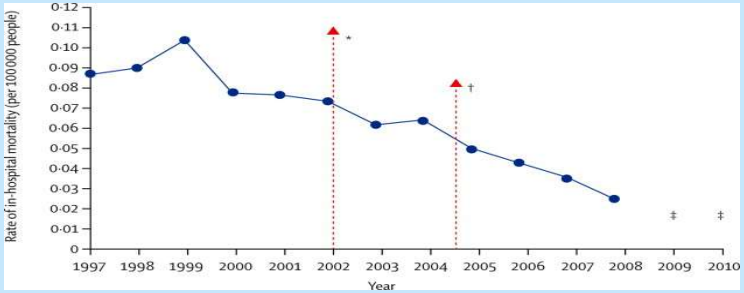


Castelblanco et al. Lancet ID 2014;14:813

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## Adjunctive Dexamethasone in Listeria Meningitis

45

- French nationwide prospective cohort study of 252 patients with neurolisteriosis, 13% of whom received dexamethasone (Lancet Infect Dis 2017;17:510)
  - Increased mortality in those receiving dexamethasone (48% vs. 27%)
- Dutch prospective cohort study of 162 patients with Listeria meningitis, 58% of whom received dexamethasone (eClinicalMedicine 2023;58:101922)
  - Rate of unfavorable outcome higher in those not receiving dexamethasone (72% vs. 46%)
  - Not receiving dexamethasone was associated with an increased risk of death in the multivariable analysis (OR 0.40; CI 0.19-0.84)

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## QUESTIONS

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