

## AHD – Meningitis Facilitator Guide

### Agenda:

- 1:00 – 1:15 Meningitis Theory Burst
- 1:15 – 2:00 Case 1
- 2:00 – 2:20 Questions for the expert & Break
- 2:20 – 3:10 Cases 2 & 3
- 3:10-3:30 Questions for the expert and Wrap Up

### EBM:

300 people got LPs (gold standard) for suspected bacterial meningitis. 100 patients were CSF culture positive for bacterial meningitis. Of these culture- positive patients, 56 did not have the classic triad of fever, neck stiffness, and altered mental status. What is the sensitivity of the classic triad for bacterial meningitis?

	<i>Has Disease (Gold Standard +)</i>	<i>Doesn't Have Disease (Gold Standard -)</i>
<i>Test Positive</i>	<i>44 (True Positives)</i>	
<i>Test Negative</i>	<i>56 (False Negatives)</i>	

- $Sensitivity = TP / (TP + FN) = 44 / (44 + 56) = 0.44$
- *The classic triad of fever, neck stiffness, and altered mental status is only 44% sensitive*
- *Learning point: Almost all patients with bacterial meningitis present with at least 2 of the 4 symptoms – headache, fever, neck stiffness, and AMS (GCS < 14). If a patient has none of these symptoms then there is a high negative predictive value.*

### Case 1

A 28-year-old man presents with a 2-day history of severe headache localizing to the back of the head. He associates nausea, emesis, and light sensitivity. He recently had an episode of sinusitis. No recent travel. He has no past medical/surgical history. He takes ibuprofen PRN, and has been using regularly during the past 24 hours for headache. He has no allergies to medications. He is an industrial engineer. He is sexually active with women only and always uses barrier protection.

VS: 101.8 °F, BP 134/82, HR 95, RR 13, and 98% on RA.

General: Patient appears uncomfortable with headache.

HEENT: Endorses photophobia with eye exam. PERRL. EOMI. No papilledema on non-dilated examination. There is mild, bilateral maxillary sinus tenderness.

Lungs: CTAB, normal effort

CV: RRR, normal S1 and S2, no m/r/g

Neuro: AOx4 without confusion. There are no focal findings.

Skin: He has no rashes, oral or genital ulcers.

*The Kernig (inability to allow full knee extension when hip is flexed to 90 degrees) and Brudzinski (spontaneous flexion of the hips during attempted passive neck flexion) signs might come up in conversation here. Neither of these tests are useful in ruling in or ruling out bacterial meningitis. The only test that might have diagnostic utility is the jolt accentuation test (patient with headache quickly turns head from side to side and test is positive if headache worsens), which has a high negative LR.*

### 1. What is on your differential diagnosis?

- Bacterial / viral meningitis – Table 1 of appendix lists most common organisms
- Drug-induced meningitis (NSAID's, Bacrim – suspected type 1 & 3 hypersensitivity)
  - o Moris G, Garcia-Monco JC. The Challenge of Drug-Induced Aseptic Meningitis. Arch Intern Med.1999;159(11):1185–1194. doi:10.1001/archinte.159.11.1185
- Inflammatory conditions (Behcet syndrome, SLE, sarcoidosis)
- Lyme disease
- Subarachnoid hemorrhage, Subdural hemorrhage, CNS malignancy
- Sinusitis, mastoiditis, spinal epidural abscess, brain abscess

### 2. What diagnostics would you obtain?

IDSA recommended studies:

- Blood cultures: 53% prevalence of bacteremia in cohort of 118 adults with acute bacterial meningitis
  - o N. Proulx, D. Fréchette, B. Toye, J. Chan, S. Kravcik; Delays in the administration of antibiotics are associated with mortality from adult acute bacterial meningitis, QJM: An International Journal of Medicine, Volume 98, Issue 4, 1 April 2005, Pages 291–298 [full-text](#))
- CBC, BMP, serum glucose, consider CRP
  - o Ask learners: why do you need to check a serum glucose?
    - Compare to the CSF glucose. If ratio of CSF glucose : serum glucose < 0.4 then bacterial meningitis is likely. (80% sensitive, 98% specific)
  - o Normal CRP has high-NPV for bacterial meningitis in the context of negative CSF gram stain (IDSA Grade B-II)
- Lumbar puncture: opening pressure, cell count with differential, CSF glucose, CSF protein, CSF gram stain and culture.
  - o Enteroviral PCR may reduce length of hospital stay, use of antibiotics, and ancillary diagnostic testing (IDSA Grade B-II)

### 3. Does this patient need a head CT before LP?

- No, this patient does not need an LP.
- Indications for head CT prior to LP:
  - o H/o CNS diseases
    - Includes those associated with CSF shunts, hydrocephalus, or trauma, those occurring after neurosurgery, or various space-occupying lesions.
  - o New-onset seizures, <1 week
  - o Immunocompromised state
    - Includes HIV/AIDS, immunosuppressive therapy, or hx transplantation
  - o Suspicious signs of increased intracranial pressure or space-occupying lesions
    - Papilledema
    - Focal neurologic signs (i.e. abnormal LOC, gaze palsy, abnormal visual fields, facial palsy, arm drift, leg drift, abnormal language)
  - o Moderate-to-severe impairment of consciousness (GCS <10)
    - an inability to answer 2 consecutive questions correctly or to follow 2 consecutive commands

4. You perform a Lumbar Puncture. What CSF studies would you order for each tube?

Cell count #1	Gram stain & culture	Chemistry: protein, glucose	Cell count #2	Other tests: eg. Viral PCR
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Case 1 continued.

Labs:

\ 14.2 /  
8.2 ----- 335  
/ 44 \

Differential shows left shift. (ask learners: what is a left shift? Bands, not neutrophilia!)

135 | 102 | 11 /  
----- 110  
4.0 | 24 | 0.8 \

Hepatic panel: normal

CRP: 55mg/L (N: 1-10 mg/L)

Serum glucose: 98 @ 12:00PM

CSF analysis @ 12:00PM

Opening pressure: 2200 mm H<sub>2</sub>O (normal: 70-200 mm H<sub>2</sub>O)

WBC: 1200/μL with 60% neutrophils, 40% lymphocytes (N:0-5/μL (0-5× 10<sup>6</sup>/L))

Glucose: 30 mg/dL (N: 40-80 mg/dL)

Protein: 350 mg/dL (N: 15-60 mg/dL)

Gram stain: see QR code (*Strep pneumoniae*)

Culture: processing



5. What is your assessment of the above labs?

Facilitators, emphasize bacterial vs viral meningitis based on LP. Refer to tables 2 and 3 of the appendix.

CBC is normal but has a left shift. CRP, while non-specific, is elevated and suggests an inflammatory state. CSF analysis reveals an elevated opening pressure, elevated WBC with neutrophilic pleocytosis, low glucose (<40% of simultaneously measured serum glucose), and high protein, which is consistent with bacterial meningitis. Gram stain is concerning for pneumococcal meningitis. **Can reference the common organisms listed in table 1 of the appendix and Tables 2 & 3 for interpretation of CSF.**

Diagnostic accuracy of CSF parameters for diagnosis of bacterial meningitis

- Lactate > 3.5 mmol/L had sensitivity 100%, specificity 100%
- CSF glucose/blood glucose ratio < 0.35 had sensitivity 92%, specificity 100%
- neutrophils > 260 cells/mm<sup>3</sup> had sensitivity 92%, specificity 100%
- leukocytes > 388 cells/mm<sup>3</sup> had sensitivity 81%, specificity 92%
- protein > 1,934 mg/L had sensitivity 88%, specificity 100%
- Reference - Eur J Clin Microbiol Infect Dis 2015 Oct;34(10):2049

**6. What is your initial management? Write the initial admission orders including doses of any medications.**

*Start antibiotics ASAP after diagnosis of bacterial meningitis is suspected or proven. Empiric antibiotics indicated if LP is delayed or purulent meningitis. Empiric treatment is based on likely pathogens.*

*Admission orders for our case: **Reference figure 1 of the appendix for EPIC orders.***

- IV vancomycin 15-20 mg/kg q8-12h with goal serum trough of 15-20 mg/L
  - o Indication: for ceftriaxone-resistant *S. pneumonia*
- IV ceftriaxone 2g q12h or 4g q24h (OR IV cefotaxime 8-12g/day with q4-6h dosing)
  - o Indication: for *S. pneumoniae*, *H. influenzae*, *Neisseria meningitides*
- IV dexamethasone 0.15 mg/kg q6h for 2-4 days
  - o First dose 10-20 minutes before or with first antibiotic dose
  - o Decreases CNS inflammation that leads to lower mortality, fewer short-term neurologic sequelae, and decreased hearing loss in pneumococcal meningitis when used as adjunctive therapy in developed countries. (CCJM article 2014)
  - o Recommended in all adults with suspected/proven pneumococcal meningitis (IDSA Grade A-I). Insufficient data to recommend in adults with meningitis by other pathogens (IDSA Grade B-III).
- Preventative measures recommended by CDC
  - o Droplet precautions for hospitalized patients as soon as diagnosis is suspected through the first 24 hours of antimicrobial therapy (CDC 2007 PDF)
  - o Chemoprophylaxis for close contacts of patients with *N. meningitidis*
    - Defined as: closer than 3 ft for >8 hrs OR those exposed to oral secretions and exposed during the 7 days prior to and 1 day after start of antibiotics
    - Rifampin 600 mg q12h for 2 days, OR ciprofloxacin 500 mg single dose, OR ceftriaxone 250 mg IM single dose
    - Reference - *N Engl J Med* 2006 Oct 5;355(14):1466 full-text

*Duration of therapy: **See Table 5 in Appendix***

**Questions for the expert:** *For meningococcal meningitis, what is the close contacts prophylaxis prescribing recommendation? For suspected pneumococcal meningitis, should we be giving rifampin with dexamethasone? Can you detail when and/or why a CSF lactate would be useful? IDSA recommends not to give dexamethasone to adults who have already received antibiotic therapy (IDSA Grade A-I). What does this mean for treatment? Must all therapy be completed inpatient or can patients transition to outpatient therapy? What are the indications for repeat LP in bacterial meningitis?*

**Break!**

**Case 2**

65-year-old female with PMHx of HTN and SLE complicated by nephritis presents to the ED with headache, fever, nausea and vomiting for 2 days. She associates lightheadedness, photophobia and neck pain. She is in a monogamous relationship with a male partner. She is retired but babysits for two school-age grandkids, but neither has been sick. She does not smoke or drink alcohol. Medications include ASA, lisinopril, and cyclophosphamide. She has no allergies to medications.

**1. What is on your differential diagnosis? How would you use your physical exam to support/refute your concerns?**

- Assess for focal neurologic deficits, mental status changes, signs of elevated ICP
- Meningeal signs are not reliable for diagnosing or ruling out meningitis.
  - o *Prospective study of meningeal signs: Clin Infect Dis 2002 Jul 1;35(1):46 full-text*
    - Nuchal rigidity: 30% sensitive, 68% specific, 26% PPV, 73% NPV
    - Kernig sign: 5% sensitive, 95% specific, 27% PPV, 72% NPV
    - Brudzinski sign: 5% sensitive, 95% specific, 27% PPV, 72% NPV
    - Positive likelihood ratios for all 3 signs ranged from 0.94-0.97
- GU exam for herpetic lesions (present in 85% of cases of herpes encephalitis)
- Rashes – Neisseria often has purpuric rash. Viral illnesses with aseptic meningitis can also have various rashes

**Case 2 continued.**

*Physical exam:*

Vitals: 100.8°F, BP 125/84, HR 64, RR 18, 99% RA

Gen: Ill appearing but in no acute distress

HEENT: PERRL, EOMI, no papilledema on non-dilated fundoscopic exam

Neck: Neck stiffness, + Kernig, + Brudzinski (*see figure 2 in appendix*)

CV: RRR, no murmurs

Lungs: CTAB, normal effort

Abd: Scaphoid, soft, nontender

GU: No lesions/rashes

Neuro: CN intact, strength 5/5, sensation intact, DTRs 2+

Skin: Dry skin, no rashes

**2. Initial labs including CBC, BMP, INR, and CRP are all normal. You are concerned about meningitis, what is the next best diagnostic step for this patient?**

- Immunocompromised (this patient is immunocompromised on cyclophosphamide)
- You should obtain a head CT
- You should start empiric antibiotics prior to obtaining the head CT so as not to delay therapy.
  - o *Note: complete sterilization of the CSF can occur within 2 hours for N meningitides and within 4 hours for S pneumoniae after starting antibiotic therapy, but antibiotic therapy should not be delayed if a LP cannot be done expeditiously*

**3. What therapy will you start?**

*Meningitis, bacterial or viral, is highly suspected. The patient is immunocompromised and over the age of 50. As such, would start:*

- IV vancomycin for ceftriaxone-resistant *S. pneumoniae*
- IV ceftriaxone for *S. pneumoniae*, *H. influenzae*, *Neisseria meningitides*
  - o *3<sup>rd</sup> gen cephalosporins are bacteriocidal with good CNS penetrance and coverage of typical organisms*
- IV ampicillin 2g q4hrs for *Listeria monocytogenes*
  - o *Indicated as empiric therapy for patients > 50 years old or immunocompromised*
- Would you give IV acyclovir to cover HSV, VZV? Can discuss. **\*\*Consider question for the expert**

- *Per IDSA, give empiric acyclovir to all patients with meningoencephalitis pending outcome of diagnostic studies (Grade A-III), with dosage 10 mg/kg IV every 8 hours (IDSA Grade A-I) (Clin Infect Dis 2008 Aug 1;47(3):303 full-text)*
- *Would you give IV dexamethasone? Can discuss. \*\*Consider question for the expert*

**4. The CT Head is negative for recent or remote stroke, hemorrhage, intracranial lesions, or herniation. After multiple attempts by several providers in the ED and on medicine, CSF is unable to be obtained. IR is unavailable currently. Discuss the course of therapy that you would prescribe for this patient.**

- *This is a great question/discussion for the expert. In this case where there is a high suspicion for meningitis at the presentation, but we are unable to obtain CSF for culture what do we do? First, look at the blood cultures – if they are positive then this can guide your course of therapy. If the blood cultures are also negative, then you likely need to commit the patient to a full course of antibiotics to adequately cover *N meningitidis*, *S pneumo*, and *Listeria*. Depending on index of suspicion for HSV, you might also commit her to a full course of acyclovir.*

**Reference tables 4-6 of the appendix for bacterial organisms based on patient population, treatment, and duration of therapy.**

**Case 3**

An 80-year-old woman with history of HTN, DM2, and hypothyroidism is hospitalized for a 1-day history of AMS and fever. Her family notes that yesterday she seemed confused and had trouble getting dressed. This morning, extremely somnolent, and she was transported to the hospital by ambulance. She takes Lisinopril, metformin, and levothyroxine. She has no medication allergies. Per family, she is independent of ADL's and manages her own finances well. She lives with her son and grandchildren but has no sick contacts. She does not drink alcohol, smoke or have risky behaviors.

*Physical exam:*

VS: 101.2 °F, 118/78, HR 110/min, RR 24/min, and 98% on RA.

Gen: Appears ill. She responds to deep stimulation with a grimace.

Neuro: Oriented to name only. Does not follow commands. She moves all extremities spontaneously.

Face is symmetric without droop, speech is clear, PERRL, no papilledema on non-dilated fundoscopic exam. Unable to flex neck, + Kernig, + Brudzinski (*see figure 2 in appendix*)

GU: No lesions or rashes

Skin: warm, dry, no rash.

Cardiovascular, pulmonary, and abdominal exam are normal.

*Labs/Diagnostics:*

CT Head: No intracranial hemorrhage or mass. No lesions identified. Normal ventricular size. Chronic small vessel ischemic changes noted.

CBC: 4.8 > 12.7 / 37 < 287 with normal differential

CMP: normal

CRP: 8mg/L (N: 1-10 mg/L)

UA: no WBC, negative nitrite, no protein

Serum glucose: 98 @ 11:00AM

CSF analysis @ 11:00AM

Opening pressure: 80 mm H<sub>2</sub>O (normal: 70-200 mm H<sub>2</sub>O)

WBC: 11/ $\mu$ L with 60% lymphocytes, 40% neutrophils (N:0-5/ $\mu$ L (0-5 $\times$  10<sup>6</sup>/L))

Glucose: 66 mg/dL (N: 40-80 mg/dL)

Protein: 76 mg/dL (N: 15-60 mg/dL)

Gram stain: no organisms

Culture: processing

HSV PCR: negative

Blood cultures: processing

**1. Discuss your differential diagnosis for this patient.**

- *Aseptic Meningitis*
  - o *Non-polio enterovirus as most common causes (coxsackie, echovirus)*
  - o *HSV 1, 2*
  - o *VZV (more often in immunocompromised patients)*
  - o *Arbovirus (West Nile may have neurologic deficit such as asymmetric flaccid paralysis)*
  - o *HIV (eg CSF: WBC 55, lymphocytic, glucose 70, pressure 80mmH2O, protein 149)*
- *Encephalitis (viral etiologies above)*
- *Early bacterial meningitis*
  - o *S. pneumoniae, N. meningitides, L. monocytogenes*
- *Atypical bacterial causes e.g. Lyme, TB, syphilis, cat scratch disease, RMSF*
- *Inflammatory / Autoimmune*
  - o *Malignancy e.g. lymphomatous meningitis, carcinomatous meningitis*
  - o *Autoimmune (rare at this age) e.g. sarcoidosis, SLE*
  - o *CNS vasculitis*
- *Delirium*
  - o *Infectious, medication, etc*
- *Vascular*
  - o *Stroke*

**2. Appropriate empiric therapy is started. MRI Head is obtained. What is the diagnosis and management?**



*Diagnosis is HSV encephalitis. >90% of cases are HSV 1. Etiology can be primary infection, reactivation of latent disease, and potentially from reinfection with a second HSV strain. MRI is recommended for all patients with encephalitis. CNS HSV type 1 infection causes a necrotizing infection of the temporal lobes. Localization of inflammation to one or both temporal lobes on neuroimaging strongly suggests HSV encephalitis. The sensitivity and specificity of CSF HSV PCR is >95%. However, early infection the PCR may be falsely negative. If suspicion for HSV encephalitis is high, then acyclovir should be continued with repeat CSF HSV PCR 3 to 7 days later. Treatment is with IV acyclovir 10 mg/kg q8h for duration of 14-21d.*

*Treatment with acyclovir has reduced mortality from 70% to about 8%-28%.*

**Questions for the expert. End AHD.**

## Appendix

**Table 1: Most common organisms for meningitis**

Organisms	
Bacterial	Viral
<i>Streptococcus pneumoniae</i> (~50%)	Enterovirus
<i>Neisseria meningitidis</i> (~25%)	HSV 1, 2
Gram-negative bacilli	HIV
Staph. Species	Arthropod-borne viruses (eg – WNV)
<i>Listeria monocytogenes</i> **	VZV, EBV
<i>Pseudomonas aeruginosa</i>	

\*\*Risk factors for *Listeria meningitis*: age >50, pregnancy, immunocompromised, ETOH

**Table 2: Bacterial vs Viral CSF analysis**

Test	Bacterial	Viral
Opening pressure	High	Normal – high
WBC	Very high; Neutrophilic	High; Lymphocytic
Glucose	Low	Normal
Protein	High	Normal – High
GC / Culture	GS+ >60%; Cx+ >80%	Negative

**Table 3: CSF profiles**

Cerebrospinal Fluid Profiles					
Investigation	Normal	Bacterial	Viral	Tuberculosis	Fungal
Opening pressure	10-20 cm (50-180 mm H <sub>2</sub> O)	High	Normal/high	High	High/very high
Color	Clear	Cloudy	Clear/cloudy	Cloudy/yellow	Clear/cloudy
Cells	< 5 mm <sup>3</sup>	1,000-50,000 mm <sup>3</sup>	50-1,000 mm <sup>3</sup>	50-500 mm <sup>3</sup>	0-1,000 mm <sup>3</sup>
Differential	Mononuclear	Neutrophilic	Lymphocytic	Mononuclear	Mononuclear
Glucose	> 45 mg/dL (2.5 mmol/L)	< 40 mg/dL (2.2 mmol/L)	> 45 mg/dL (2.5 mmol/L)	< 45 mg/dL (2.5 mmol/L)	> 45 mg/dL (2.5 mmol/L)
Protein	< 45 mg/dL	100-500mg/dL	< 200 mg/dL =	50-300 mg/dL	> 45 mg/dL

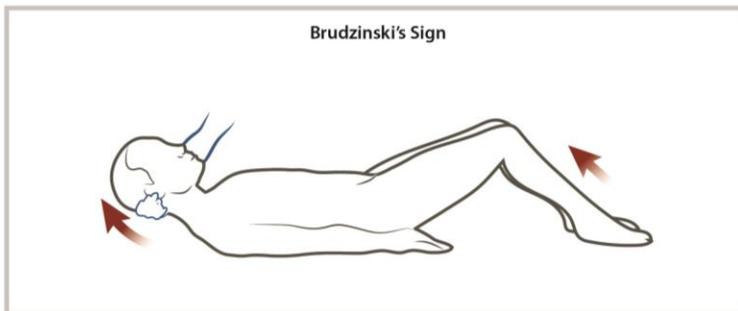
**Figure 1: EPIC Inpatient CSF labs order set**

CSF Labs Panel
✓ Accept

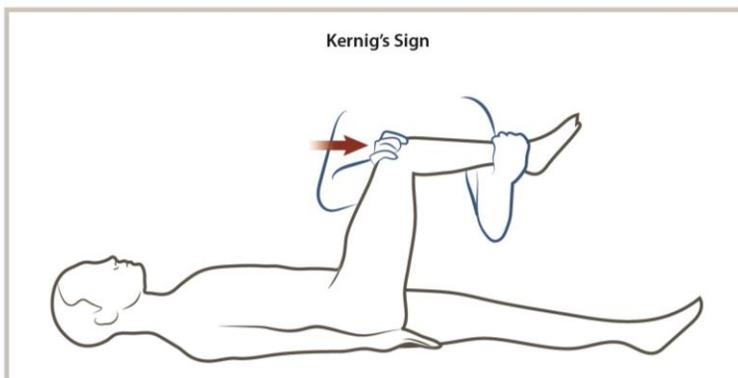
- Tube 1: Cell Count, CSF**  
 STAT, Once First occurrence Today at 1429 P
- Tube 2: Glucose, CSF**  
 STAT, Once First occurrence Today at 1429 P
- Tube 2: Protein, CSF**  
 STAT, Once First occurrence Today at 1429 P
- CSF Culture Plus Stain**  
 STAT, Once First occurrence Today at 1429 P
- Tube 4: CSF Cell Count (Hold for additional studies)**  
 STAT, Once First occurrence Today at 1429 P
- Cryptococcal Ag, CSF w/Fungal Cult**  
 STAT, Once
- Enterovirus RNA, Qualitative RT PCR, CSF**  
 STAT, Once First occurrence Today at 1430 P
- Herpes Simplex 1 & 2, Real-time PCR, CSF**  
 STAT, Once
- West Nile Virus, CSF**  
 STAT, Once First occurrence Today at 1430 P
- Acid Fast Culture Plus Stain**  
 STAT, Once

ⓘ Next Required
✓ Accept

**Figure 2: Kernig and Brudzinski sign**



1. Lift patient's neck toward his or her chest. Brudzinski's sign is positive when neck flexion causes patient to flex knees and hip.



1. Flex hip and knee 2. Extend knee while keeping hip flexed. Kernig's sign is positive when pain is elicited upon extension of the knee.

**Table 4: Antibiotics and organisms**

Antibiotic	Organism coverage
Vancomycin	Resistant <i>S. pneumoniae</i>
Ceftriaxone	<i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>Neisseria meningitidis</i>
Ampicillin	<i>Listeria monocytogenes</i>
Acyclovir	HSV, VZV

**Table 5: Duration of treatment based on identified pathogen**

Organism	Treatment duration
<i>H. influenzae</i>	7 days
<i>N. meningitidis</i>	7 days
<i>S. pneumoniae</i>	10-14 days
<i>S. agalactiae</i>	14-21 days
aerobic gram-negative bacilli	21 days
<i>L. monocytogenes</i>	at least 21 days

IDSA 2004 recommendations (IDSA Grade A-III)

**Table 6: Common bacterial organisms based on patient population**

Population	Organisms
2-50 years old	<i>S. pneumoniae</i> ; <i>N. meningitis</i>
>50 years old	<i>S. pneumoniae</i> ; <i>N. meningitis</i> ; <b>Listeria</b> , aerobic gram (-) bacilli
Post-neurosx; CSF shunt	CoNS, <i>S. aureus</i> , aerobic gram (-) bacilli
Skull fracture	<i>S. pneumoniae</i> , <i>H. influenzae</i> , group A strep
Penetrating trauma	CoNS, <i>S. aureus</i> , aerobic gram (-) bacilli
Asplenic	<i>S. pneumoniae</i> , <i>N. meningitis</i> , <i>H. influenzae</i>