Team Medicine

#17

CNS Infections

Writer: Rayan AlZuhairi
Reviser1: Tarfah Al-Obaidan
Reviser 2: Anoof Eshky

Leader: Sama Al Ohali

■ Slides ■ Doctors notes ■ Additional

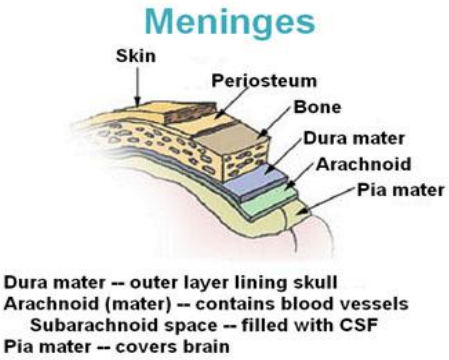
431 Teams

❖ Introduction (variable causes and outcome):

- **CNS infections have variable causes and outcomes that can range from acute benign form of viral meningoencephalitis to a rapidly fatal bacterial meningitis with local progressive mental deterioration and death, it depends on:**
  - **Etiological organism (giving the wide spectrum of clinical disease)**
  - **Time of starting the appropriate antibiotic therapy: (delayed therapy causes a bad outcome.)**
  - **Use of steroids.**

❖ Definitions:

- **Meningitis – inflammation of the meninges. (pia mater, arachnoid and surrounding CSF)**
- **Encephalitis – inflammation of the brain parenchyma.**
- **Meningoencephalitis – inflammation of brain + meninges.**
- **Aseptic meningitis – inflammation of meninges with sterile CSF (-ve culture)**
- **Meninges?**



Dura mater -- outer layer lining skull
Arachnoid (mater) -- contains blood vessels
Subarachnoid space -- filled with CSF
Pia mater -- covers brain

A) Meningitis:

Definition: Inflammation of the meningeal membranes that cover the brain and spinal cord.

CAUSES OF MENINGITIS:

INFECTIOUS	NON-INFECTIOUS
Viral	**Aseptic Meningitis**
Bacterial	**Malignancy**
Mycobacterial	**Sarcoidosis**
Brucella	**behcet disease (vasculitis)**
Fungal	**SLE**

❖ Types of meningitis: (bacterial or aseptic)

❖ Aseptic Meningitis:

- **CSF: pleocytosis 100s (particularly an increase in white blood cell), Normal Glucose & Protein , -ve Culture.**

- **Causes:**

-Enteroviruses: most common cause 80%
-HSV-2, and other viruses
-Acute HIV
-Partial Rx Bacteria; if somebody was on oral Abx presented to you with meningitis then you do CSF and find it –ve culture you have to think of Aseptic meningitis.
-Drugs: MTZ (Metronidazole), **TMP-SMX** (Trimethoprim/Sulfamethoxazole), **NSAIDs, Antiepileptic: carbamazapine, IVIG** (Intravenous Immunoglobulin).

❖ Symptoms of Bacterial Meningitis:

- **High grade sudden fever**
- **Severe Headache**
- **Altered level consciousness, irritability, photophobia**
- **Nausea/Vomiting. (Increased ICP)**
- **Seizures (in extreme cases)**
- **Stiff neck**

❖ Signs of Bacterial Meningitis:

- **Vital signs (always in clinical exam start with VS).**
- **Febrile**
- **Hemodynamics.**
- **Nuchal rigidity.**
- **Kerning's sign: while patient is lying supine, with the hip and knee flexed to 90 degrees pain limits passive extension of the knee**
- **Brudzinski's sign: flexion of the neck causes involuntary flexion of the knee and hip**
- **Don't forget: ears, sinuses, chest..etc.**
- **Petechiae**
- **Papilledema.**

- **So, absence of <u>all</u> three sings of classical triad of meningitis which are:**
  - **Fever**
  - **Stiff neck**
  - **Changes in mental status (<u>more common in bacterial than viruses</u>)**
    ((Makes the diagnosis of meningitis unlikely))
  - ❖ **Kerning's and Brudzinski's sign have very low sensitivity**
    So it is rarely to find them but it is highly specific.
  - ❖ **What is the <u>most useful Sign</u> telling you that the patient does not have the disease?**

- Jolt accentuation maneuver: ask patient to rapidly rotate his or her head horizontally; Headache worsens.
- Sensitivity of 100%, specificity of 54%, positive likelihood ratio of 2.2, and negative likelihood ratio of 0 for the diagnosis of meningitis.

So if it is –ve → the patient does not have meningitis.

❖ Complications:

- **Hydrocephalus.**
- **Seizures.**
- **SIADH.**
- **Subdural effusions & empyema.**
- **Septic sinus or cortical vein thrombosis.**
- **Arterial ischemia / infarction (inflammatory vasculitis).**
- **CNS Palsies (esp. deafness)**
- **Septic shock / multi-organ failure from bacteremia (esp. meningococcus & pneumococcus)**
- **Risk of adrenal hemorrhage with hypo-adrenalism (Waterhouse-Friderichsen syndrome)**

❖ Investigations:

- **CBC, Creatinine, Electrolytes: Na+**
- **Blood Culture**
- **CXR**
- **CT Head**
- **CSF analysis (Lumbar puncture)**

Be careful:

☒ **Increase ICP may increase risk of brain herniation**
☒ **Cellulitis at area of lumbar puncture**
☒ **Bleeding disorder**

- **Cell count with differential**
- **Glucose, protein**
- **CSF appearance (Clear/turbid)**
- **Gram stain (most imp *within 30 mns*)**
- **Culture (24-48 hrs)**
- **TB AFB smear PCR and culture**
- **Brucella serology and PCR**
- **HSV PCR**
- **Cryptococcus antigen**

In certain situations

❖ CSF Finding suggesting Bacterial Meningitis:

– **It is done when gram stain is -ve**

TABLE IV

CFS FINDINGS SUGGESTING BACTERIAL MENINGITIS WHEN INITIAL GRAM STAIN IS NEGATIVE[1]

CSF leukocyte count > 1,000/mm³
CSF leukocyte count > 100 mm³, of which > 50 per cent neutrophils
CSF glucose < 30 mg/dl
CSF glucose/blood glucose ratio < 40 per cent
CSF protein > 200 mg/dl
Raised serum C-reactive protein

Note: Consider alternative diagnosis, eg tuberculous, fungal or viral meningitis, or brain abscess. Treat initially as bacterial meningitis. These figures are not applicable to neonates.

If you have anyone of these it suggests Bacterial Meningitis.
It is important to know is it bacterial or viral to start antibiotics crucially.

Bacterial Pathogens:

Age group	Organisms
neonates	Group B Streptococci 49%, E coli, enterococci, Klebsiella, Enterobacter, Salmonella, Serratia, Listeria
Older infants and children	Neisseria meningitidis, S. pneumoniae, M. tuberculosis, H. influenzae
Adult	Streptococcus pneumonia 37% Neisseria meningitides13% Listeria monocytogenes10% Other strept.species 7% Gram negative 4% Haemophillus influenza 4% TB, Brucella (in chronic meningitis)

❖ Important points to keep in mind:

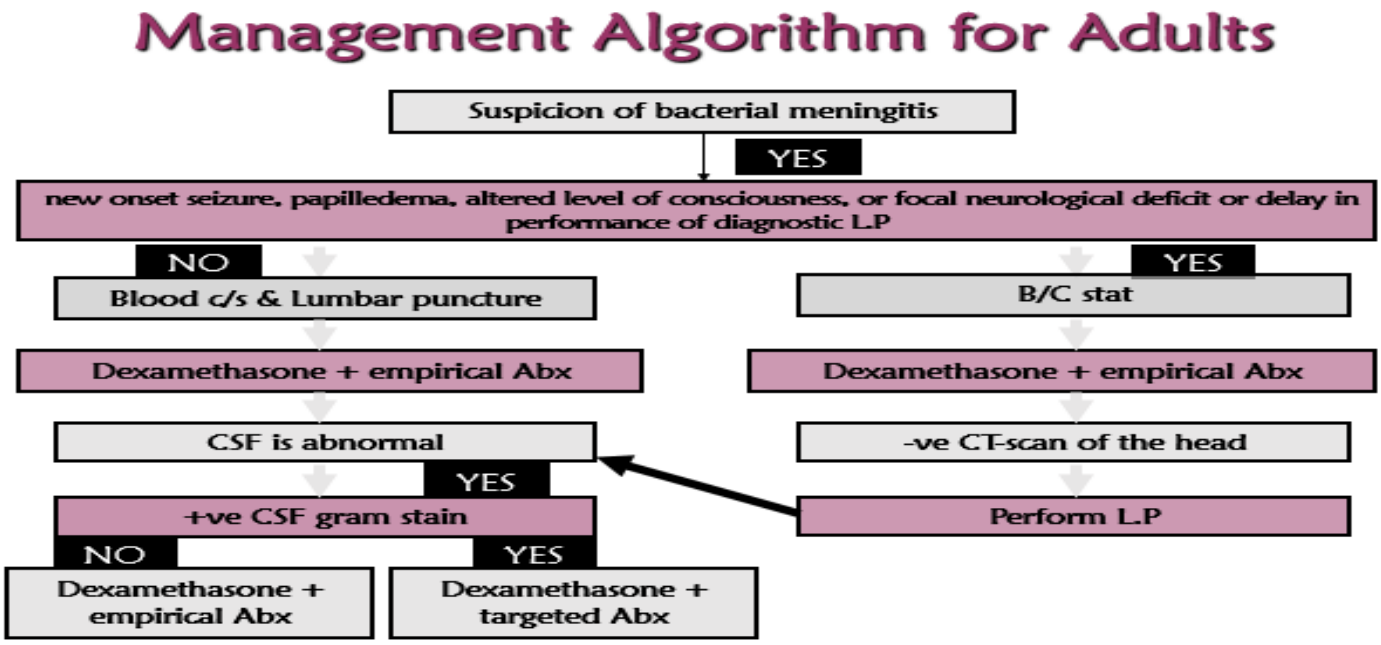
- Global emergence and prevalence of Penicillin- Resistant Streptococcus pneumonia.
- Dramatic Reduction in invasive Hemophillus influenza disease secondary to use of conjugate Haemophillus Type B- vaccine.
- Group B – Streptococci: Neonate, emerging as disease of elderly nowadays.

❖Empiric Treatment of Bacterial Meningitis:

- **DON'T FORGET MENINGEAL DOSES**
- Ceftriaxone 2gm IV Q12h
  -To reach high CSF levels
- Vancomycin 500-750mg IV Q6h (to cover the possibility of highly penicillin resistant pneumococcus)
- Dexamethasone (0.15mg/kg IV Q6h) for 2-4 days : 1st dose 15-20 min prior to or con-comitant with 1st dose Abx to block TNF production.
- Ampicillin (for Listeria).

Three Antibiotics + Dexamethasone = EMPIRIC TREATMINT
Why Dexamethasone instead of TNF Blockers? It is unknown cause but there are many clinical trial studies showed that the great effect of Dexamethasone.

❖ **Management: important**



B) Encephalitis/Encephalopathy:

- **Most common cause: Herpes simplex.**
- **Diagnosis: +ve PCR**
- **Treatment: Acyclovir (IV for 3 weeks)**
- **Other common causes:**
  - **Arboviruses. Eg: Dengue (some body travel to Jeddah often comes back with features of encephalitis we think of Dengue).**
  - **Rabies (from infected bats or dogs).**
  - **Listeria, Cat scratch disease and Amoeba.**

C) Brain Abscess:

- **Organisms:**
- **Streptococci (60-70%)**
- **Bacteroides (20-40%)**
- **Enterobacteriacea (25-33%)**
- **Staphylococcus Aureus (10-15%), S. Milleri**
- **Rare: Nocardia, Listeria**
- **CT brain: If abscess more than 2.5cm then surgical drainage, and if patient is neurologically unstable or decrease LOC drain regardless of size**
- **Antimicrobials: empirically Ceftriaxone with metronidazole, otherwise according to susceptibility**
- **Duration until response by neuroimaging (not for 2 weeks as meningitis)**

D) Subdural Empyema:

- **In adults 60-90% are extension of:**
- **Sinusitis**
- **Otitis media**

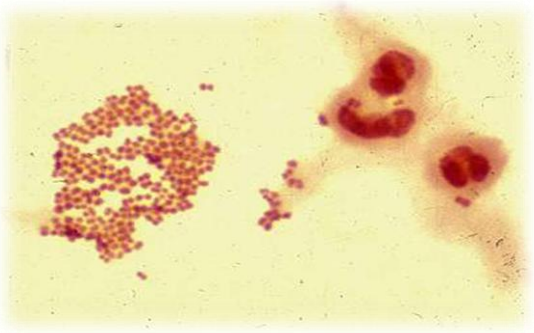
- **Surgical emergency: must drain**
- **Abx same as brain abscess**

Case1:

A 34 years old man returning from Hajj presented to ER with fever, severe headache, neck stiffness, and vomiting for two days. He was found confused by his family. His vital signs were as following: Temperature 38.4, HR 110, and BP 100/70. Clinical examination revealed obtunded man with nuchal rigidity, petechiae all over his body and positive kerning's and brudzinski's signs.

Investigations:

- **CSF examination:**
  Opening pressure: 260 mm H20 & cloudy
  WBC: 1500/ ml: 96% polymorphs
  Glucose: 24mg / dl
  Protein: 200 mg
- **Gram stain:**



gram-negative diplococcic (Neisseria meningitides- meningococcus)

People who are from Africa we have to think of N.meningitides.

Prevention (vaccination):

- **Conjugate meningococcal vaccine: A, C, Y, W135 (menactra) (Serogroup B still no vaccine)**
- **Up to 3 years in adult: Does not affect nasopharyngeal carriage and does not provide herd immunity.**

Meningococcus:

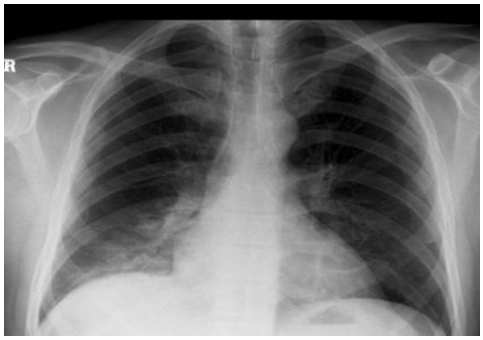
- **Fulminate meningococcemia with purpura ➡ overwhelming sepsis, DIC (Disseminated intravascular coagulation)**
- **Meningitis with rash (petechiae)**
- **Meningitis without rash**
- **Total mortality of 3-10%**

Treatment & chemoprophylaxis:

- Droplet Isolation: 48h post Abx
- Treatment: Ceftriaxone 7 days
  - Eradicate nasopharyngeal carriage: house hold contact (to kill the bacteria in nasopharyngeal stage before it reached CNS)
  - Health care providers who examined patient closely
- Rifampin 600 mg for 2 day or Ciprofloxacin 500mg once or Ceftriaxone 125mg I.M once

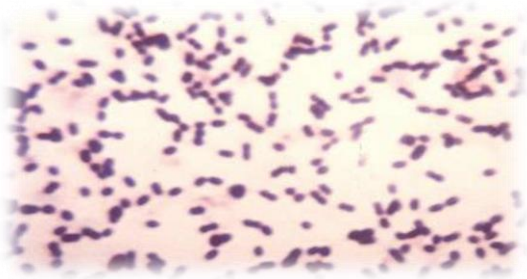
Case 2:

A 26-year-old Saudi female presents with fever, cough and headache for the last 3 days. Examination revealed ill-looking woman with sign of consolidation over lower lungs. CXR showing bilateral lower zone consolidation. Six hours after admission, her headache became worse and rapidly became obtunded.



Investigations:

- CSF examination:
  - WBC: 3000; 99% PML
  - Sugar: zero
  - Protein: 260 mg/dl
- Gram stain:



Gram-positive diplococcic
(S. pneumonia –pneumococcal)

Epidemiological features of pneumococcal meningitis:

- The most common cause
- Highest mortality 20-30% (most deadly worse than N. meningitides)
- May be associated with other focus: pneumonia, otitis media, sinusitis
- Head trauma and CSF leak
- Splenectomy and SS disease
- Global emergence of Penicillin-Resistant

Treatment and prevention of Pneumococcus meningitis:

- Penicillin G (only if MIC less than 0.1) *Minimum inhibitory concentration*
- Ceftriaxone 14 days (if MIC 0.1-1)
- Vancomycin if Highly penicillin resistance (if MIC is 2 or above)
- Steroids (Dexamethasone) (pre Abx)
- Vaccination: Pneumococcal conjugate vaccine, Pneumococcal polysaccharide vaccine

Case3:

A 70-year-old man with malaise, anorexia loss of weight of 7 kg over 1 month. He underwent colonoscopy prior to symptoms onset. Watery diarrhea 4 times a day for 1 week, fever, chills and headache for 3 days, double vision for 2 days. Neck stiffness, jolt accentuation, 6th CN palsy.

Investigations:

- **CSF examination:**
  - **Cloudy**
  - **WBC: 1000 70% lymphocytes**
  - **Glucose: 50mg / dl**
  - **Protein: 170 mg**
- **Gram stain:**

Gram-positive bacilli listeria monocytogenes

Listeria Monocytogenes:

Risk groups:

- **Age <1y or >50y**
- **Alcoholics**
- **Pregnancy: up to 30%**
- **immunocompromised 70 %**

Routes of transmission:

- **Mainly food borne**
- **Transplacental /vertical**
- **Cross contamination (nursery)**
- **Inoculation (skin) farmers**
- **colo/sigmoidoscopy→ bacteremia/meningitis (up to 5% healthy :Normal flora)**

Listeria Monocytogenes meningitis treatment:

- **Ampicillin 2gm IV Q4h**
- **21 day duration (3 weeks)**

#Listeria and TB are the only two meningitic diseases that cause 6th CN palsy.

Case4:

A 56-year-old Indian man presented to the infectious disease clinic with low grade fever and night sweats for 6 weeks and headache for 4 weeks. Temperature 38.2C, speaking well. He had opthalmoplegia, neck stiffness and bilateral papilledema.

Low grade fever + night sweats for 6 weeks (more chronic presentation) suggest TB.

Investigations:

- **CSF examination:**
  - **Xanthocromic (yellowish appearance of CSF)**
  - **WBC 340 L: 85%**
  - **Protein 1.5 g**
  - **Sugar 25 mg**
  - **AFB: diagnostic yield increase to 87% when four serial specimens examined**
  - **Culture: gold standard**
  - **PCR: specificity 98%**

Treatment:

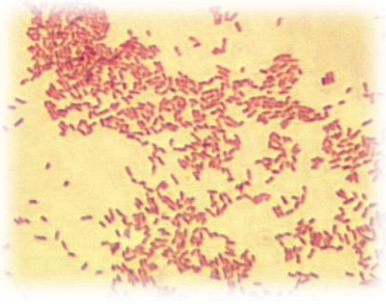
- **Antibiotic chemotherapy ➡ CSF concentrations:**
  - **INH, Pyrazinamidine, pass freely into the CSF**
  - **Rifampicin has 10% the concentration as in plasma**
  - **Streptomycin do not pass BBB in absence of inflammation**
- **Steroids in TB meningitis:**
  - **Treatment with dexamethasone is associated with a reduced risk of death (unknown why it is used)**

Case5:

30-year-old Saudi sheepherder with 3 weeks headache blurred vision. Looks uncomfortable, temperature 38.1C, and Jolt accentuation present.

Investigations:

- **CSF examination:**
  - **CSF pleocytosis 105 mostly lymphocytes**
  - **Brucella PCR in CSF positive**
  - **Brucella titre 1:320**
- **Blood culture:**
  - **Grew brucella species**



Gram-negative coccobacilli brucella

Treatment:

Doxycycline, Rifampin, TMP-SMX

Case6:

46-year-old gentleman with fever for 1 week. Headache for 3 days. Aortic valve replacement 6 years ago. Fever 39.1C, stiff neck. CT showed brain abscess.

Investigations:

Blood culture: Staphylococcus Aureus
TEE: vegetation aortic valve

Diagnosis:

Meningitis secondary to endocarditis with septic emboli to the brain.

Treatment:

Drainage of brain abscess: shows Staph. Aureus
Treatment: Cloxacillin IV, flagyl

Summary

1. CNS infections vary from a mild self-limiting infection to a potentially fatal infection requiring emergent treatment. It can be encephalitis, meningitis or meningioencephalitis.

2. **Meningitis can be:**
   - **Bacterial** (Cloudy CSF) or **Aseptic** (Clear CSF)
   - **Acute** (Within hours to days) or **Chronic** (Within weeks to months)

3. **Aseptic meningitis:** Meaning meningitis not caused by pyogenic bacteria. The cause can be from a **non-infectious process** (Autoimmune, Drug-Induced, Neoplastic and Immune-mediated) or from an **infectious agent** (Viral, Mycobacterial, Parasitic and Fungal).

4. **Bacterial Meningitis:** Caused by bacteria inducing a pyogenic inflammatory response in the CSF.

5. **Clinical Presentation** (It may be difficult to differentiate between aseptic and bacterial clinically):
   -**Symptoms:** (The **characteristic triad for Acute Bacterial Meningiti**s: Fever, Nuchal Rigidity & Change in mental status). **Other Symptoms:** Photophobia, Headaches, N/V and Seizures.
   -**Signs:** Rashes, Cranial nerve palsies, Kerning's sign & Brudzinski's sign (Both highly specific) and Jolt Accentuation Maneuver (100% sensitivity).
   -Look for **signs and symptoms of increased ICP** (N/V, seizures, Papilledema, Ocular Palsies, Headaches, Back Pain and altered mental status).

6. **Complications of Bacterial Meningitis:**
   -**Local:** Seizures, Coma, Brain Abscess and Subdural Empyema
   -**Distant:** DIC, Respiratory Arrest, Waterhouse-Friderichsen syndrome.
   -**Permanent:** CNS palsies (Deafness), Hydrocephalus and Brain Damage.

7. **Investigations**: Routine blood work, Blood culture (Before Antibiotics), CXR, Head CT and CSF Examination (LP).

8. **CSF findings in bacterial meningitis** show a pyogenic inflammatory response: Cloudy appearance, Elevated WBC count (PMNs), low glucose, high protein and positive gram stain. Findings **in Aseptic meningitis** show a non-pyogenic response: Lymphocytic pleocytosis, normal or slightly elevated protein, normal glucose, CSF appears normal (May be positive in: serology, PCR, AFB smear or culture)

9. **Organisms in Acute Bacterial Meningitis:** (The most common cause of meningitis is Strept. Pneumoniae)
-**Neonates:** Group B strept., E.coli, Listeria Monocytogenes
-**Infants & Children:** N. meningitidis, Strept. Pneumoniae and H. Influenza.
-**Adults:** Strept. Pneumoniae, N. meningitidis and H. Influenza.
-**Elderly:** Strept. Pneumoniae, N. meningitidis and Listeria.

10. The **Empiric Treatment** for Bacterial Meningitis = **Dexamethasone + 3 Antibiotics** (Ceftriaxone, Ampicillin & Vancomycin).

11. The **most common cause of Encephalitis is HSV**. It is diagnosed by **PCR** and treated with **Acyclovir** (2-3 weeks).

12. A **Brain Abscess** is mostly caused by **Streptococci**. A **subdural empyema** requires **emergent** drainage. Both are treated with the same Antibiotics (Metronidazole and Ceftriaxone).

13. **Meningococcal Meningitis**: Meningitis caused by **N. Meningitidis** (Gram –Ve diplococcic). Purpura rashes are classic for Meningococcal meningitis. Transmissible by throat and respiratory secretions. **Tx:** Ceftriaxone.

14. **Pneumococcal meningitis:** The most common cause of meningitis is **Strept. Pneumoniae** (Gram +ve diplococcic). It has the highest mortality rate (20-30%). **Tx:** Ceftriaxone, Penicllin G or Vancomycin.

15. Only **Listeria and TB** meningitis cause **6Th Cranial Nerve Palsy**. **Listeria** is most commonly food borne (bowls) and is common in elderly, neonatal and immunocompromised (70%) patients. **Tx:** Ampicillin. **TB Meningitis** gives CSF a xanthocromic appearance. **Tx:** isoniazid, rifampicin, pyrazinamide and streptomycin.

16. **Brucella** species are common in sheepherders. Detected by PCR or culture. **Tx:** Doxycycline, Rifampin, TMP-SMX.

Questions

1. **A 35-year-old Patient walked into the ER with a 3-day history of neck stiffness and fever. The patient appeared to be disoriented and soon lost consciousness. You need to order a LP to confirm bacterial meningitis as the diagnosis. You were informed that the procedure was delayed several hours. What is your next step?**

   A. Order a blood culture to confirm diagnosis.
   B. Wait for LP.
   C. Treat for Bacterial Meningitis until LP can be obtained.
   D. A&B

   Answer: "C "
   If LP has anticipated delays, treat first and don't wait.

2. **All of the following are causes of Aseptic meningitis EXCEPT:**

   A. Enterovirus
   B. Sarcoidosis
   C. Methotrexate
   D. N. Meningitidis
   E. SLE

   Answer: "D"
   It causes a pyogenic inflammatory response.

3. **The characteristic triad of symptoms in acute bacterial meningitis is**:

   A. Malaise, photophobia and back pain.
   B. Fever, photophobia and headaches.
   C. Fever, alteration in mental status and neck stiffness.
   D. Headaches, nausea and vomiting.

   Answer: "C"

4. **Regarding clinical signs of Meningitis. Which one of the following signs is highly specific for meningitis:**

   A. Papilledema
   B. Kerning's sign
   C. Jolt Accentuation Maneuver
   D. Purpura

   Answer: "B"
   Remember highly specific means not all the cases have this symptom. But if they do have the symptom,
   they definitely have the disease (it is specific for a disease). Highly sensitive means everyone with the disease has the symptom but other diseases have the symptom too.

5. **A boy with a suspected case of acute bacterial meningitis underwent a lumbar puncture, and the diagnosis was confirmed. All of the following are CSF examination findings that indicate bacterial meningitis except:**

   A. Low glucose
   B. High protein
   C. High count of Lymphocytes
   D. High count of PMNs
   E. Cloudy CSF

   Answer: "C"
   It is a characteristic of Aseptic meningitis.

6. **Which of the following is not true about Streptococcus Pneumoniae?**

A. It is the most common cause of bacterial meningitis.
B. It has a 20-30% mortality rate.
C. CXR is particularly important in diagnosis.
D. It causes purpura rashes.

Answer: "D"
N. Meningitidis causes purpura rashes.

7. **Steroids are given in CNS infection to manage which of the following:**

A. Hydrocephalus
B. Brain Abscess.
C. Deafness.
D. Cerebral Edema

Answer: "D"
Steroids are given to reduce the inflammation and therefore reduce the accumulation of fluid in the brain.

8. **A man diagnosed with bacterial meningitis is complaining that he became acutely ill and that he is bleeding from his nose and mouth. Clinical Exam revealed tachycardia and hypotension. What did this man develop?**

A. Sepsis
B. Subdural Empyema
C. DIC
D. Respiratory arrest

Answer: "C"
A strong infection like meningitis can induce SIRS that could lead a patient to develop DIC. DIC causes bleeding from the mouth, gums, nose and other areas. It also causes bruising.

9. **Based on the last question, which type of meningitis does this man most likely have?**
10.

A. Pneumococcal meningitis
B. Meningococcal Meningitis
C. Aseptic Meningitis
D. Mycobacterial Meningitis

Answer: "B"
The most common cause of DIC is infection with gram –ve sepsis.

11. **Regarding Encephalitis, which term best describes the proper approach in management?**

A. Supportive care + Antiviral therapy
B. Anticonvulsants + Steroids
C. A&B
D. Acyclovir

Answer: "C"