



# CNS Infections

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## Objectives:

- Be familiar with clinical presentation of disease
- Appreciate different causative organisms
- Approach to management
- Utilization of antimicrobial therapy
- How to prevent disease
- Role of Steroids
- Case discussion

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## References:

**Slides - Black**

**Doctor's notes - Red**

**Master the boards/Kumar and Clark's**

**Extra explanation - Grey**

## Optional:



CNS Infections

[Editing file](#)

## Definitions:

- Meningitis: inflammation of the meninges ( inflammation of the pia mater and the arachnoid mater, with suppurat\* of the cerebrospinal fluid)
- Encephalitis: infection of the brain parenchyma
- Meningoencephalitis: inflammation of brain + meninges
- Aseptic meningitis: inflammation of meninges with sterile CSF

## ❖ Encephalitis/Encephalopathy

### Causes:

- Herpes simplex:
  - Diagnose with PCR,
  - Treat with Acyclovir
- Arboviruses:
  - For example: Dengue "حمى الضنك"
- Rabies
- Rare:
  - *Listeria*, cat scratch disease, and amebic.



## ❖ Meningitis

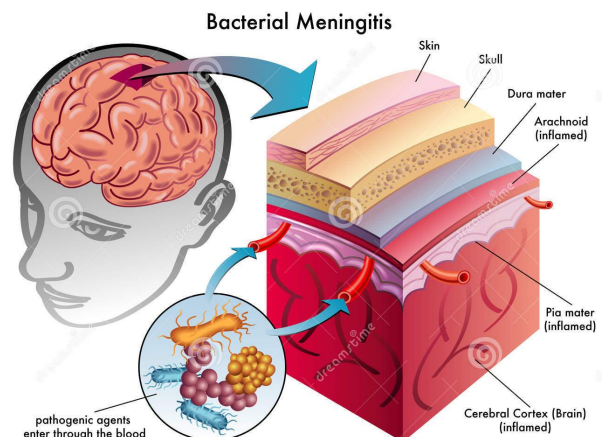
### Variable causes and outcome:

- Acute Benign Forms of Viral Meningoencephalitis
- Rapidly Fatal Bacterial Meningitis with local progressive mental deterioration and death
- Different etiological organisms
- Time of starting appropriate therapy

### Refresh your memory:

The brain meninges are formed of 3 layers, from outermost to innermost (DAP):

1. Dura mater
2. Arachnoid mater
3. Pia mater



## ❖ Causes of meningitis:

| INFECTIOUS    | NON-INFECTIOUS     |
|---------------|--------------------|
| Viral         | Aseptic Meningitis |
| Bacteria      | Malignancy         |
| Mycobacterial | Sarcoid            |
| Brucella      | Behcet disease     |
| Fungal        | SLE                |

# 1) Aseptic Meningitis

## Characteristics:

- **CSF analysis:**
  - **Pleocytosis\* (100s),**
  - **Normal Glucose and Protein**
  - **Negative Culture**

## Causes:

- **Enteroviruses: most common cause (80%)**
- HSV-2, and other viruses. (dengue, zika, chikungunya, yellow fever)
- HIV
- Partial Rx Bacteria (partially treated bacterial meningitis) **the second most common**
- Drugs: Metronidazole, TMP-SMX, NSAIDs, carbamazepine, IVIG (IV immunoglobulin)
- Rare: leptospirosis\*

Bridge to pathology: Behcet's disease is a rare type of vasculitis caused by an autoimmune response most likely after an exposure to the following organisms:

- Herpes simplex virus
- Strep, staph
- E-Coli

It manifests with oral aphthous ulcers, genital ulcers and uveitis.



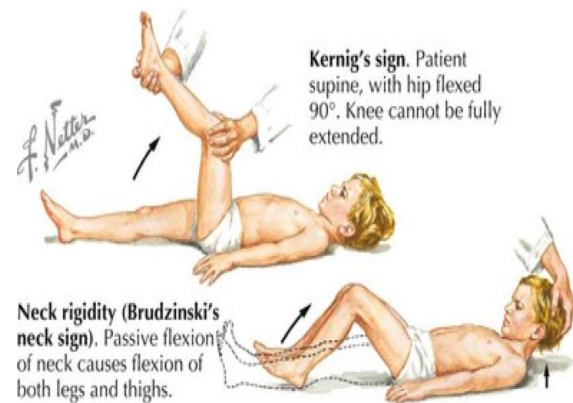
# 2) Bacterial Meningitis

## Symptoms:

- **High grade sudden fever**
- **Severe** Headache
- Altered level consciousness (more common in bacterial than viral meningitis), irritability, **photophobia**
- Vomiting
- Seizures
- **Stiff neck**
- **Bulging fontanel in infants**

## Signs:

- **Vital signs: Fever (38 degrees and above)**
- **Nuchal rigidity** (Inability to flex the neck forward)
- **Kernig's sign:** while patient is lying supine, with the hip and knee flexed to 90 degrees pain limits passive extension of the knee due to lower back pain or neck pain.
- **Brudzinski's sign:** passive flexion of the neck causes involuntary flexion of the knee and hip
- **Most useful (sensitive) sign is Jolt accentuation maneuver:** ask patient to rapidly rotate his or her head horizontally → Headache worsens.
- Papilledema **due increased ICP.**
- Neurological deficit (**cranial nerves**)
- Don't forget source of infection: ears, sinuses, chest..etc
- Petechiae, ecchymosis (**DIC**). with Neisseria meningitidis



Absence of all 3 signs of the classic triad of:

- Fever.
- Neck stiffness.
- An altered mental status.

**virtually eliminates** a diagnosis of meningitis

\*Pleocytosis: the presence of abnormally large amounts of lymphocytes in the CSF

**Bridge to microbiology:** Enteroviruses are: Coxsackievirus A and B, Echovirus, Enterovirus subtypes, Human rhinovirus and Poliovirus

\*Leptospirosis is a bacterial disease that affects humans and animals. It is caused by bacteria of the genus *Leptospira*. It spreads through the urine of infected animals, which can get into water or soil and can survive there for weeks to months. Many different kinds of wild and domestic animals carry the bacterium.



- Kernig and Brudzinski signs have low sensitivity but **high specificity**
- Jolt accentuation maneuver: **Sensitivity of 100%**, specificity of 54% with a positive likelihood ratio of 2.2, and negative likelihood ratio of 0 for the diagnosis of meningitis. **So if it's not there, you can rule out the disease.**

### ❖ Complications:

- **Hydrocephalus**
- **Seizures**
- **SIADH**
- **Subdural effusions and empyema**
- **Septic sinus or cortical vein thrombosis**
- **Arterial ischemia / infarction (inflammatory vasculitis)**
- **CN Palsies**
  - **The most common neurological deficit of untreated bacterial meningitis is 8th cranial nerve deficit/deafness.**
- **Septic shock / multi-organ failure from bacteremia (especially meningococcus and pneumococcus)**
- **Risk of adrenal hemorrhage with hypoadrenalism (Waterhouse-Friderichsen syndrome)**

### ❖ Investigations:

- **CBC, Creatinine (to assess renal function to fix antibiotics) electrolytes: Na (in case of SIADH)**
- **Blood Culture**
- **CXR (chest infection)**
- **CT Head**
- **CSF analysis (missing)**
- **Appearance, opening pressure**

**Bridge to pathology:** In Waterhouse-Friderichsen syndrome, bacterial infection (usually due to Neisseria meningitidis) leads to massive hemorrhage into one or (usually) both adrenal glands. It is characterized by overwhelming bacterial infection meningococcemia leading to massive blood invasion, organ failure, coma, low blood pressure and shock, disseminated intravascular coagulation (DIC) with widespread purpura, rapidly developing adrenocortical insufficiency and death.



- **Cell count is in the 1000's, neutrophils mostly (>50%)**
- **Protein level elevated**
- **Glucose level decreased**
  - **CSF glucose <30 mg/dl**
  - **CSF glucose/blood glucose ratio < 40%**



**Remember to be careful:**

- **ICP may increase risk of herniation.**
- **Cellulitis at area of lumbar puncture.**
- **Bleeding disorder.**

### ❖ **The best initial test and most accurate test is an LP (lumbar puncture)**

| Cerebrospinal Fluid Evaluation |                               |                                |                      |                      |
|--------------------------------|-------------------------------|--------------------------------|----------------------|----------------------|
|                                | Bacterial meningitis          | Cryptococcus, Lyme, Rickettsia | Tuberculosis         | Viral                |
| Cell count                     | 1000s neutrophils             | 10s-100s lymphocytes           | 10s-100s lymphocytes | 10s-100s lymphocytes |
| Protein level                  | Elevated                      | Possibly elevated              | Markedly elevated    | Usually normal       |
| Glucose level                  | Decreased                     | Possibly decreased             | May be low           | Usually normal       |
| Stain and culture              | Stain: 50-70%<br>Culture: 90% | Negative                       | Negative             | Negative             |

**Bridge to microbiology:** the reason glucose level is decreased in bacterial meningitis is because bacteria tend to utilize sugar at high rates.

❖ **Bacterial Pathogens:**

| Age group                  | Organism   |
|----------------------------|--|
| Neonates                   | <ul style="list-style-type: none"> <li>● <b>Group B Streptococci* 49%</b></li> <li>● <b>E coli</b>, enterococci</li> <li>● <b>Klebsiella</b>,</li> <li>● <b>Enterobacter</b>,</li> <li>● <b>Samonella, Serratia, Listeria</b></li> </ul>   |
| Older infants and children | <ul style="list-style-type: none"> <li>● <b>Neisseria meningitidis</b></li> <li>● <b>S. pneumoniae</b></li> <li>● <b>M.tuberculosis, H.influenzae</b></li> </ul>   |
| Adults                     | <ul style="list-style-type: none"> <li>● <b>Streptococcus pneumoniae 37%</b></li> <li>● <b>Neisseria meningitides 13%</b></li> <li>● <b>Listeria monocytogenes 10%</b></li> <li>● <b>Other strep.species 7%</b></li> <li>● <b>Gram negative 4%</b></li> <li>● <b>Haemophilus influenzae 4%</b></li> <li>● <b>TB, Brucella</b></li> </ul> |

**Important**



The-three major causes of neonatal meningitis are:

- **group B streptococci**
- **Escherichia coli**
- **Listeria monocytogenes**

**Bridge to microbiology:**  
 Gram + streptococcus Beta hemolysis:  
 Bacitracin sensitive: group A (Strep pyogenes)  
 Bacitracin resistant: Group B (Strep agalactiae)



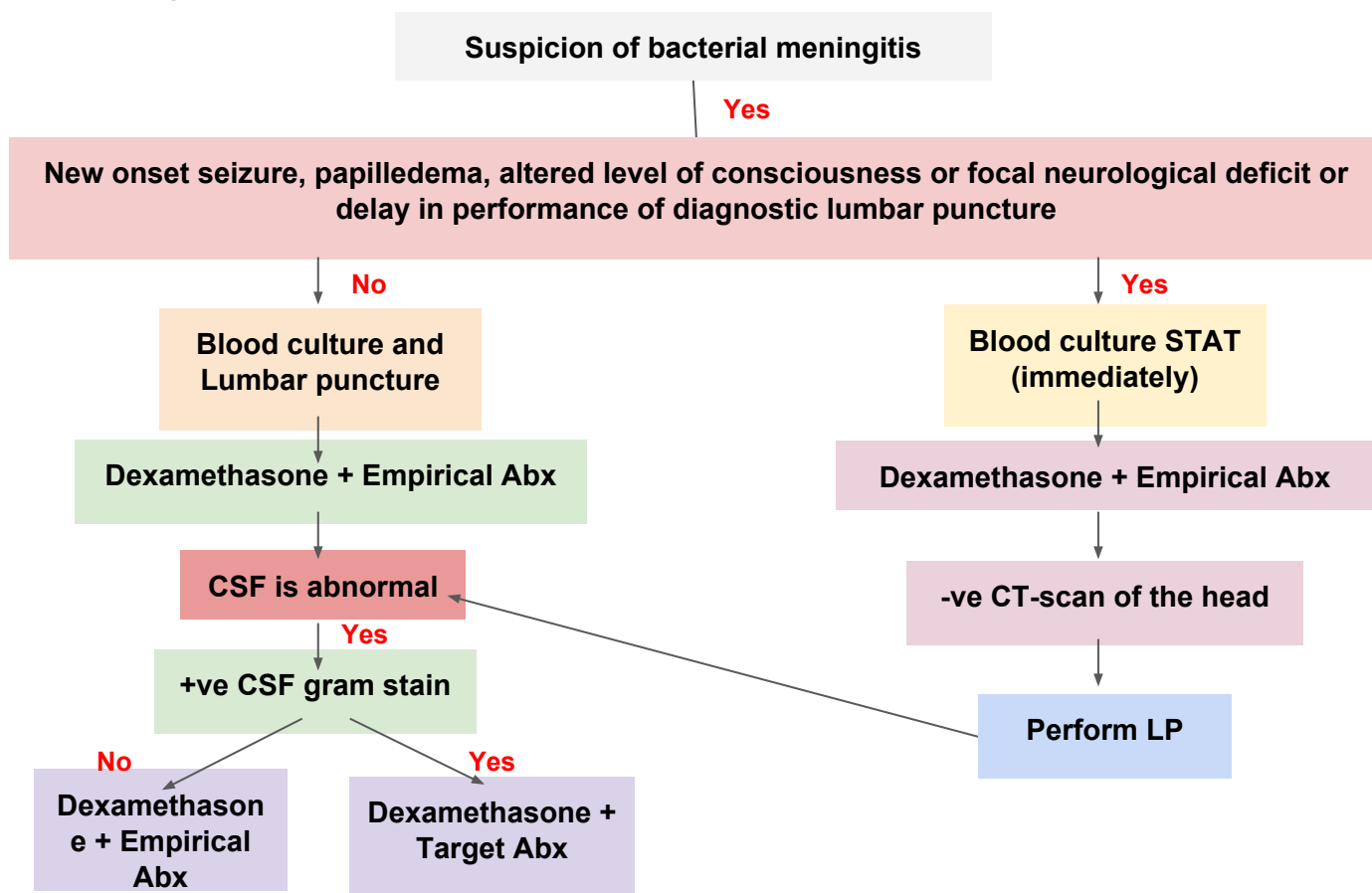
- Global emergence and prevalence of Penicillin-resistant *Streptococcus pneumoniae*
- Dramatic Reduction in invasive *Haemophilus influenzae* disease secondary to use of conjugate *Haemophilus Type B- vaccine*.
- **Group B Streptococci**: previously in neonate, now emerging as disease of elderly

❖ **Treatment:**

- Empirical antibiotics in meningeal doses:
  - **Ceftriaxone**
  - **Vancomycin** (highly penicillin resistant *pneumococcus*)
  - Dexamethasone for 2-4 days : 1<sup>st</sup> dose 15-20 min prior to or concomitant with 1<sup>st</sup> dose  
**Abx to block TNF production**
  - Add Ampicillin (for *Listeria*)

\*Gram + streptococcus alpha hemolysis: Optochin sensitive: strep.pneumoniae

## Management in Adults



| Brain Abscess   | Subdural Empyema   |
|---|--|
| <ul style="list-style-type: none"> <li>● Organisms:               <ul style="list-style-type: none"> <li>○ <b>Streptococci</b> (60-70%), <i>Bacteroides</i> (20-40%), <i>Enterobacteriaceae</i> (25-33%), <i>S.Aureus</i> (10-15%), <i>S.Milleri</i>.</li> <li>○ Rare: <i>Nocardia</i>, <i>Listeria</i></li> </ul> </li> <li>● CT brain: If abscess more than 2.5cm then surgical drainage. And if patient neurologically unstable or decrease LOC drain regardless of size</li> <li>● Antimicrobials: empirically <b>Ceftriaxone with metronidazole</b> (For anaerobes), otherwise according to susceptibility</li> <li>● Duration until response by neuroimaging</li> </ul> | <ul style="list-style-type: none"> <li>● In adults 60-90% are extension of:               <ul style="list-style-type: none"> <li>○ <b>Sinusitis</b></li> <li>○ <b>Otitis media</b></li> </ul> </li> <li>● Surgical emergency: must drain</li> <li>● Abx same as brain abscess</li> </ul> |

| Clues to answering the “most likely diagnosis” question |              |
|---|--------------|
| Symptom   | Diagnosis    |
| Stiff neck, photophobia, meningismus                    | Meningitis   |
| Confusion   | Encephalitis |
| Focal neurological findings                             | Abscess      |

## Cases

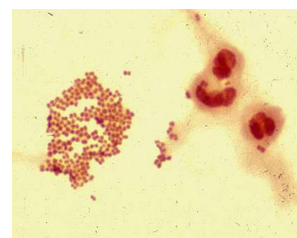
Case 1

34 years old man returning from Hajj came with:  
Fever, severe headache, neck stiffness, vomiting for two days  
Found confused by family

In ER: Temp 38.4, HR 110, BP 100/70  
Obtunded, Nuchal rigidity, Kernig's and brudzinski's signs, **Petechiae**



CSF examination:  
Opening pressure: 260 mm H2O & cloudy  
WBC: 1500/ ml: 96% polymorphs  
Glucose: 24mg / dl  
Protein: 200 mg  
Gram stain: **negative diplococci**



Diagnosis: meningococcal meningitis (**neisseria meningitidis**)

Management:

Droplet Isolation (prevent exposure to patient's droplets): 48h post Abx

Treat with **Ceftriaxone** or **Penicillin G** for **7 days**

Eradicate nasopharyngeal carriage: household contact, Health care providers who examined patient closely give **chemoprophylaxis**: Rifampicin for 2 d or Ciprofloxacin once or Ceftriaxone I.M once

**Pregnant woman: ceftriaxone**

**Bridge to history:** During the Hajj season back 1987-1988, a group of pilgrimage people from India who were carrying Neisseria Meningitidis infected a lot of people during Hajj and caused an outbreak in different areas such as Sudan and then it spread to the rest of the world. That's why the pre-Hajj vaccination was introduced in the early 1990's. Vaccines were targeted on serogroups A,C because these were the serogroups that caused the outbreak. 10 years later: Quadrivalent conjugate meningococcal vaccine: A, C, Y, W135 (menactra) came along to target all serogroups. Immunity up to 3 years in adult: Does not affect nasopharyngeal carriage and does not provide herd immunity



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**

6 hours after admission, her headache became worse and rapidly became obtunded (Mentally clouded or dulled).



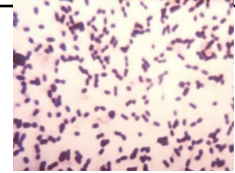
CSF:

WBC: 3000 : 99% PML

Sugar: Zero (The bacteria consumes the glucose)

Protein: 260 mg/dl.

Gram stain: **gram positive diplococci pneumococcus**



Diagnosis: *Pneumococcal meningitis*

- **The most common cause** (because it's associated with distant site infections)
- Highest mortality 20 – 30%
- May be associated with other Focus: Pneumonia, Otitis Media, Sinusitis
- Head Trauma & CSF Leak
- Splenectomy and Sickle cell disease
- Global emergence of Penicillin – Resistant

Treatment:

- Steroids (pre Abx)
- Penicillin G MIC\* < 0.1mcg/ml → Penicillin G
- Penicillin G MIC 0.1-1 → Ceftriaxone for **14 days**
- Penicillin G MIC ≥ 2mcg/ml (if Highly penicillin resistant) → Vancomycin and ceftriaxone

\*MIC: Minimum Inhibitory Concentration

- Vaccination:
- Pneumococcal polysaccharide vaccine (Pneumovax): 23 purified capsular polysaccharide antigens (serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F) **you don't have to remember the numbers**
- Pneumococcal conjugate vaccine (Pneumovax 13): Valent conjugate vaccine for children
- PPSV is recommended (routine vaccination)
- **For both children and adults in special risk categories:**
  - Serious pulmonary problems, eg. Asthma, COPD
  - Serious cardiac conditions, eg., CHF
  - Severe Renal problems
  - Long term liver disease
  - DM requiring medication
  - Immunosuppression due to disease (e.g. HIV or SLE) or treatment (e.g. chemotherapy or radio therapy, long-term steroid use
  - Asplenia

### Mnemonic!

Streptococcus pneumoniae causes "MOPS"

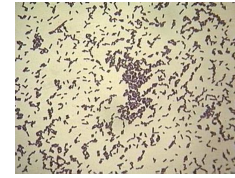
- Meningitis
- Otitis media
- Pneumonia
- Sinusitis





70 year old man with malaise, anorexia loss of weight of 7kg over 1 month Underwent Colonoscopy prior to symptoms onset, Watery diarrhea 4 times a day for 1 wk  
The patient had: fever, chills and headache for 3 days  
Double vision for 2 days, Neck stiffness, jolt accentuation, 6th CN palsy

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



Diagnosis: **Listeria Monocytogenes**

**Risk groups:**

- age <1y or >50y
- Alcoholics
- pregnancy: up to 30%
- immunocopromised 70 %

**Routes of transmission:**

- **\*mainly food borne**
- **\*transplacental /vertical**
- **\*Cross contamination(nursery)**
- **\*inoculation(skin) farmers**
- **\*colon/ sigmoidoscopy**
- **\*bacteremia / meningitis ( up to 5% healthy: Normal flora)**

**Treatment:**

- **Ampicillin +/- Gentamicin (if we suspect bacteremia)**
- **21 day duration**
- **Penicillin allergy patients: TMP-SMX or Meropenem**

Case 3

30 y Saudi **sheep herder** with 3 weeks headache blurred vision

Looks uncomfortable  
Temp 38.1  
Jolt accentuation present



- CSF pleocytosis 105 mostly lymphocytes
- Glucose and protein are normal
- Gram stain: **no organism**

Diagnosis: **Brucella**

**What will you order?**

- Brucella titre 1:320
- Brucella **PCR in CSF Detected**
- Brucella culture: no growth

**Neurobrucellosis Treatment:**

- Doxycycline
- Rifampin
- Ceftriaxone

Duration? **Different duration**

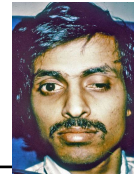
Continue until CSF is normal (3-12 months)

Case 4

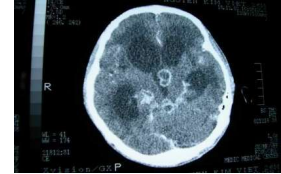
## Case 5

56 year old Indian man presented to the infectious disease clinic with low grade fever and **night sweats** for 6 wks and headache for 4 wks

T: 38.2 C, speaking well  
Ophthalmoplegia  
Neck stiffness  
Bilateral papilledema

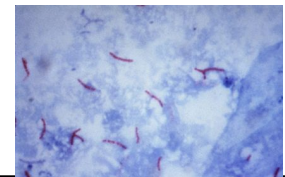


CSF: xanthochromia, WBC= 340 L: 85 %  
protein 1.5g sugar 25 mg  
Gram stain: **no organism**



What other tests can we do?

- **AFB:** diagnostic yield increase to 87% when four serial specimens examined
- use last fluid & large volume (10 to 15 mL)
- **Culture: gold standard**
- **PCR:** NAAT sensitivity %56 percent and specificity 98%



Diagnosis: TB meningitis

Treatment: CSF concentrations:

- **INH Pyrazinamide, pass freely into the CSF**
- Rifampin has 10% the concentration as in Plasma
- Streptomycin or ethionamide do not pass BBB in absence of inflammation.

32 **HIV positive** gentleman with 3 weeks history of **forgetfulness** and **change in personality** presents with generalized **seizure** to ER

After ABC and stabilization CT was done..

What test do you want?

- CD4: 77 cells/mm<sup>3</sup>
- VL: 1,340,324 cp/mL
- Toxoplasma IgG: positive
- Brain Bx: *Toxoplasma Gondii*



Diagnosis: **Toxoplasma Gondii**

Treatment:

- Pyrimethamine
- Sulfadiazine
- Folinic acid

Duration? Minimum 6 wks after resolution of signs/symptoms

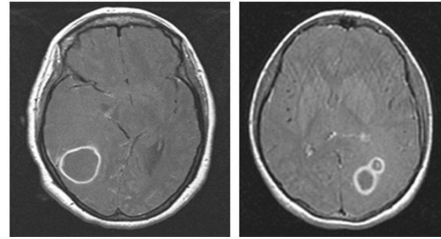
Prophylaxis:

- Primary prophylaxis:
  - TMP-SMX-DS (trimethoprim and sulfamethoxazole)
  - Can stop if CD4 > 200 for 3 months
- Chronic Suppression (secondary prophylaxis):
  - Sulfadiazine
  - Pyrimethamine
  - Folinic acid
- When to stop? CD4 > 200 for 6 months

## Case 6

46 gentleman with fever for 1 week. Headache for 3 days,  
Past medical history: Prosthetic AVR 6 years ago

T 39.4, BP 100/90, P 120, RR 22  
 Signs: Stiff neck, drowsy, papilledema



Diagnosis: Brain Abscess

Most Important Tests?

**Blood Culture:** Staphylococcus Aureus (MSSA)

**TEE:** vegetation aortic valve

Case 7

Treatment:

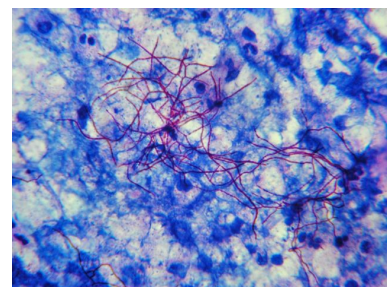
- Drainage of brain abscess: MSSA
- Redo AVR: MSSA
- Antibiotics
  - Cloxacillin
  - flagyl

Case 8

40 YO lady with SLE on azathioprine and prednisone presented with 1 wk cough, yellow sputum, SOB, 2 days of fever, and stiff neck

- O/E: looks unwell T 38.2, BP 110/50, RR 30
- Chest: R sided bronchial breathing
- CNS: Neck rigid, jolt accentuation present.
- CBC: WBC 2 Hb 9 Plt 140
- CXR: right middle lobe consolidation
- CSF WBC 100 lymphocytes, N P G
- Gram stain: **no organism seen**

Partial AFB, on modified Kinyoun stain



Other stain?

Partial AFB, on modified Kinyoun stain

Diagnosis: Nocardia

Treatment:

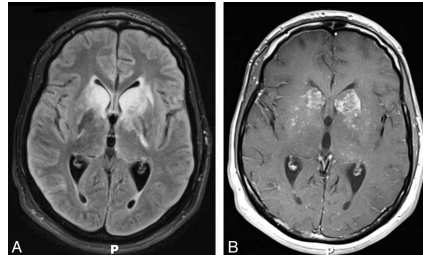
- TMP-SMX
- Imipenem
- Add amikacin when more than one organ involved
- Alternative: linezolid +meropenem

Duration:

- 3-6 wks IV therapy then change to po
- Immunocompetent: TMP-SMX, minocycline, amox/clav for 3 more months
- Immunocompromised: treat with 2 drugs for at least one year

- A 29-year-old man with HIV/AIDS and recent cryptococcal meningitis who was treated successfully
- Four months later while on fluconazole and with a CD4 count of 66 cells per microliter and an HIV viral load of 400,000 copies/mL:
  - He was started on antiretroviral therapy (emtricitabine/tenofovir/efavirenz [Atripla])
- Eight months after initiation of the antiretroviral therapy:
  - headache, stiff neck, nausea, and vomiting

Case 9



Axial FLAIR (A) and axial T1WI postcontrast (B) imaging show distention of the Virchow-Robin spaces in the basal ganglia with hyperintense signal and enhancement. These images also demonstrate that the inflammatory process has spread into the parenchyma of the basal ganglia, where high FLAIR signal and patchy enhancement are seen

**Diagnosis:**

- Fungal cultures: negative
- Cryptococcal antigen weakly positive
- Late IRIS\*: Steroids

\*Immune reconstitution inflammatory syndrome (IRIS) (also known as immune recovery syndrome) is a condition seen in some cases of AIDS or immunosuppression, in which the immune system begins to recover, but then responds to a previously acquired opportunistic infection with an overwhelming inflammatory response that paradoxically makes the symptoms of infection worse -wikipedia-

**Summary**

| Organism specific presentations/ “What is the most likely diagnosis?”                     |   |
|---|---|
| Presentation  | The most likely diagnosis is...           |
| AIDS with <100 CD4 cells/μl   | Cryptococcus                              |
| Camper/hiker, rash shaped like a target, joint pain, facial palsy, tick remembered in 20% | Lyme disease                              |
| Camper/hiker, rash moves from arms/legs to trunk, tick remembered in 60%                  | Rocky mountain spotted fever (Rickettsia) |
| Pulmonary TB in 85%   | Tuberculosis                              |
| None  | Viral                                     |
| Adolescent, petechial rash  | Neisseria                                 |

# MCQ's

**Q1: A 28-year-old junior doctor has been complaining of a headache for the last 24 hours. It started gradually, intensifying slowly and involving the entire cranium, but over the last couple of hours she has noticed that turning her head is uncomfortable. She feels generally unwell and prefers to lie in a dark room. Her friend has noticed that she seems irritable. On examination, she exhibits photophobia and there is neck stiffness. There is no papilloedema. Close examination of her skin reveals no rashes. Kernig's sign is negative. A lumbar puncture (LP) reveals low protein, normal glucose and lymphocytosis. What is the diagnosis?**

- A. Viral meningitis**
- B. Migraine**
- C. Aseptic meningitis**
- D. Bacterial meningitis**
- E. TB meningitis**

**Q2: A 23-year-old man presents to accident and emergency with a 1-day history of severe headache, discomfort when looking at the lights and neck stiffness. There is a non-blanching rash observed on his trunk. He has recently recovered from chickenpox. On examination he is pyrexial at 39°C. The most likely causative organism is:**

- A. Streptococcus pneumoniae**
- B. Listeria monocytogenes**
- C. Neisseria gonorrhoeae**
- D. VZV**
- E. Neisseria meningitidis**

**Q3: A 40-year-old IV drug addict complains of right-sided weakness and headache over the past week. He has been previously healthy and is on no prescribed medications. On physical examination, he is afebrile, cachectic, and in mild distress. His neck is supple, and his lungs and skin are clear. Cardiac examination reveals no murmur. He has a mild right hemiparesis. He is tested for HIV and found to be negative. An echocardiogram reveals no valve vegetation, which of the following is the most likely diagnosis?**

- (A) Bacterial endocarditis**
- (B) Bacterial meningitis**
- (C) Brain abscess**
- (D) Cryptococcal meningitis**
- (E) Foreign body embolus**

**Q4: A patient with nuchal rigidity and headache undergoes lumbar puncture. The CSF contains markedly increased numbers of lymphocytes, leading to a presumptive diagnosis of viral meningitis. Which of the following groups of viruses is most likely to be involved?**

- (A) Adenoviruses**
- (B) Enteroviruses**
- (C) Human papillomaviruses**
- (D) Poxviruses**
- (E) Reoviruses**

**Answers: 1.A, 2.E, 3.C, 4.B**

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**Thank you**

**If you have any question please contact with us at: 13  
Internalmedicineteam434@gmail.com**