

"He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all." – William Osler



430
MEDICINE
TEAMWORK

CNS INFECTIONS

Done By: Sara AlSukiat

CNS Infections

Introduction:

- 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
 - ✓ Time of starting the appropriate therapy : delayed therapy causes a bad outcome
 - ✓ Use of steroids

Definitions:

- Meningitis → Inflammation of the meninges (Pia, Arachnoid and Dura)
- Encephalitis → Infection of the brain parenchyma
- Meningoencephalitis → Inflammation of the brain and the meninges
- Aseptic meningitis → Inflammation of meninges with **sterile** CSF (Negative culture)

I. Meningitis

- **Definition:** Inflammation of the meningeal membranes that cover the brain and spinal cord
- **Causes:**

INFECTIOUS	NON-INFECTIOUS
<ul style="list-style-type: none"> ✓ Viral ✓ Bacterial ✓ Mycobacterial ✓ Brucella ✓ Fungal (<i>Cryptococcus meningitis is the most common fungal meningitis and usually occurs in people who are immunocompromised e.g. HIV</i>) 	<ul style="list-style-type: none"> ✓ Aseptic meningitis ✓ Malignancy ✓ Sarcoidosis ✓ Behcet disease ✓ SLE

- **Classification:** depending on onset of symptoms
 - Acute → hours to days, usually bacterial or viral causes
 - Chronic → weeks to months, usually mycobacterial, fungal, Lyme disease or parasites

- **Types of meningitis (bacterial vs. aseptic) :**

1. Bacterial meningitis:

- Medical emergency requiring a prompt recognition and antibiotic therapy.
- Bacterial pathogens (**causative organisms**): depends on age group

✓ Neonates	Group B Streptococci 49%, E. Coli, Enterococci, Klebsiella, Enterobacter, Salmonella, Serratia, Listeria
✓ Older infants & children	Neisseria meningitides, S. pneumonia, M. tuberculosis, H. influenzae
✓ Adults	Streptococcus pneumonia.....37% Neisseria meningitides.....13% <i>Listeria monocytogenes.....10%</i> <i>Other strept. species.....7%</i> <i>Gram negative.....4%</i> <i>Haemophilus influenza.....4%</i> TB, Brucella

* Group B Streptococci is found in the **birth canal**. Therefore, it is recommended that every pregnant female should be **screened** by a vaginal swab and a rectal swab at 37 weeks of gestation, if culture was positive then **IV antibiotics** should be administered at the time of delivery to prevent meningitis in her infant.
*TB and Brucella cause a more chronic form of meningitis

○ Signs and symptoms of bacterial meningitis:

• Symptoms →

1. HIGH grade sudden fever (*Low-grade with TB*)
2. Severe headache, seizures, vomiting
3. Altered level consciousness, irritability, photophobia
4. Neck stiffness

* **Classic triad** ^{IMP} of: fever, neck stiffness, and altered level of consciousness. Absence of this triad usually eliminates bacterial meningitis from the diagnosis.

• Signs →

1. Hemodynamics/vital signs (*fever +/- tachycardia and hypotension*)
2. Nuchal rigidity
3. Signs of meningeal irritation:

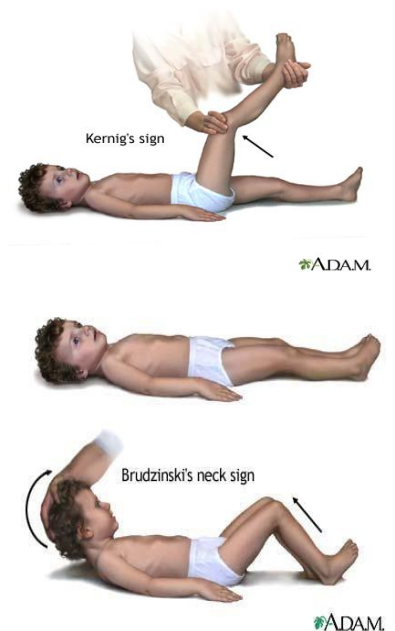
- ✓ **Kerning's sign:** while patient is lying supine, with the hip and knee flexed to 90 degrees. A positive Kerning's sign occur when pain limits passive extension of the knee.
- ✓ **Brudzinksi's sign:** flexion of the neck causes involuntary flexion of the knee and hip

- Found in only 5% of patients
- They're **highly specific** (i.e. if positive the patient definitely has meningeal irritation, so they're only useful if positive) but they're not sensitive (i.e. if they were negative you cannot exclude meningitis)

4. Don't forget: ears, sinuses, chest... (look for source of infection)
5. Petechiae and ecchymosis (*Petechial rash is more likely to occur with N. meningitides*)
6. Bulging fontanels in infants (*fontanels=soft spots on top of the infant's head*)
7. Increased intracranial pressure and its manifestation e.g. papilledema
8. Focal neurological deficits

9. **Most useful sign: Jolt accentuation maneuver** ^{IMP}

- Ask patient to rapidly rotate his or her head (left and right) horizontally; headache worsens.
- **Sensitivity of 100%** (i.e. if the patient had meningitis and while doing this maneuver his headache didn't get worse then meningitis is **excluded**, so it is only useful if negative to **RULE OUT** the disease), specificity 54% (i.e. if someone with a headache and while doing this maneuver his headache worsens does **not** mean he has meningitis), positive likelihood ratio 2.2, and negative likelihood ratio of 0 for the diagnosis of meningitis.



○ **Complications:**

- Hydrocephalus
- Seizures
- SIADH (syndrome of inappropriate anti-diuretic hormone secretion)
- Subdural effusions and empyema
- Septic sinus or cortical vein thrombosis
- Arterial ischemia/infarction (inflammatory vasculitis)
- Cranial nerve palsies (most commonly **deafness** especially in children)
- Septic shock/multi-organ failure from bacteremia (especially meningococcus & pneumococcus)
- Risk of adrenal hemorrhage with hypo-adrenalism (Waterhouse-Friderichsen syndrome)

2. Aseptic meningitis:

- Inflammation of the meninges with sterile CSF, associated with a better prognosis.
- CSF findings:
 - ✓ **Negative** culture **IMP**
 - ✓ **Normal** glucose and protein
 - ✓ Pleocytosis in 100s (<1000 WBC)
- **Causes** of **ASEPTIC** meningitis: (nonbacterial pathogens mostly viral causes)
 1. **Enterovirus**: most common cause **80%** (benign cause) **IMP**
 2. HSV-2, and other viruses
 3. HIV
 4. Partially treated bacterial meningitis **IMP**
 5. Drugs: MTZ, TMP-SMX, NSAIDS, Carbamazepine, IVIG (Intravenous immunoglobulin)
- **Treatment** → non-specific therapy other than supportive care is required (self-limited)

• Investigations of meningitis:

- CBC, Creatinine, electrolytes: Na → because meningitis is one of the causes of SIADH
- **Blood culture** can figure out the etiology in 20-30% of time without lumbar puncture **IMP**
→ Blood culture is a MUST in any febrile patient!
- CXR
- CT head (esp. if seizures or focal neurological deficits are present)
- **CSF analysis**: **IMP**
- Be careful of (relative contraindications)
 - ✓ raised ICP may increase risk of herniation
 - ✓ Cellulitis at area of lumbar puncture
 - ✓ Bleeding disorder
- Done through lumbar puncture
- Note the opening pressure
- Cell count with differential (to check the percentage of PMNs)
- Chemistry (Glucose & protein)
- CSF appearance *cloudy/turbid* is consistent with pyogenic leukocytosis
- **Gram stain**
- **Culture**
- Special tests: (if you suspect a chronic form of meningitis)
 - ✓ TB AFB smear, PCR and culture
 - ✓ Brucella serology and PCR
 - ✓ HSV PCR
 - ✓ **Cryptococcus** antigen in **HIV** patients (really high opening pressure)
- How to **differentiate** between different CSF results:
If you suspect bacterial meningitis
 - ✓ Gram stain positive? → Bacterial **IMP**
 - ✓ Gram stain negative? → The following findings are suggestive of bacterial meningitis **IMP**

Opening pressure is the initial CSF reading given during the administration of a lumbar puncture. Once the needle is inserted, a device called a manometer is used to measure the opening pressure (the pressure of the initial CSF collection) which is usually raised in bacterial meningitis.

TABLE IV
CFS FINDINGS SUGGESTING BACTERIAL MENINGITIS WHEN INITIAL GRAM STAIN IS NEGATIVE ¹
CSF leukocyte count > 1,000/mm ³ CSF leukocyte count > 100 mm ³ , 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.

- To differentiate between **ALL** types: (EXTRA summary)

	NORMAL	ASEPTIC	PYOGENIC (BACTERIAL)	TUBERCULOSIS
APPEARANCE	Crystal clear	Clear/turbid	Turbid/purulent(cloudy)	Turbid/viscous
WBC COUNT	<5	100-1000	>1,000 (1000-20000)	50-500
DIFFERENTIAL	nil	Lymphocytes & monocytes (lymphocytic pleocytosis)	Mostly polymorphs	Monocytes or lymphocytes
GLUCOSE	50-75	Normal	<40 (low)	<30 (low)
PROTEIN	<60	>100 (normal/slightly high)	>150 (high)	>150 (high)

- **Important points to keep in mind:**

- Global emergence and prevalence of Penicillin-Resistant Streptococcus pneumonia
- Dramatic reduction in invasive Hemophilus influenza disease secondary to use of conjugate Hemophilus Type B-vaccine
- Group B Streptococci: neonate, emerging as disease of elderly!

- **Bacterial meningitis clinical management approach: IMP**

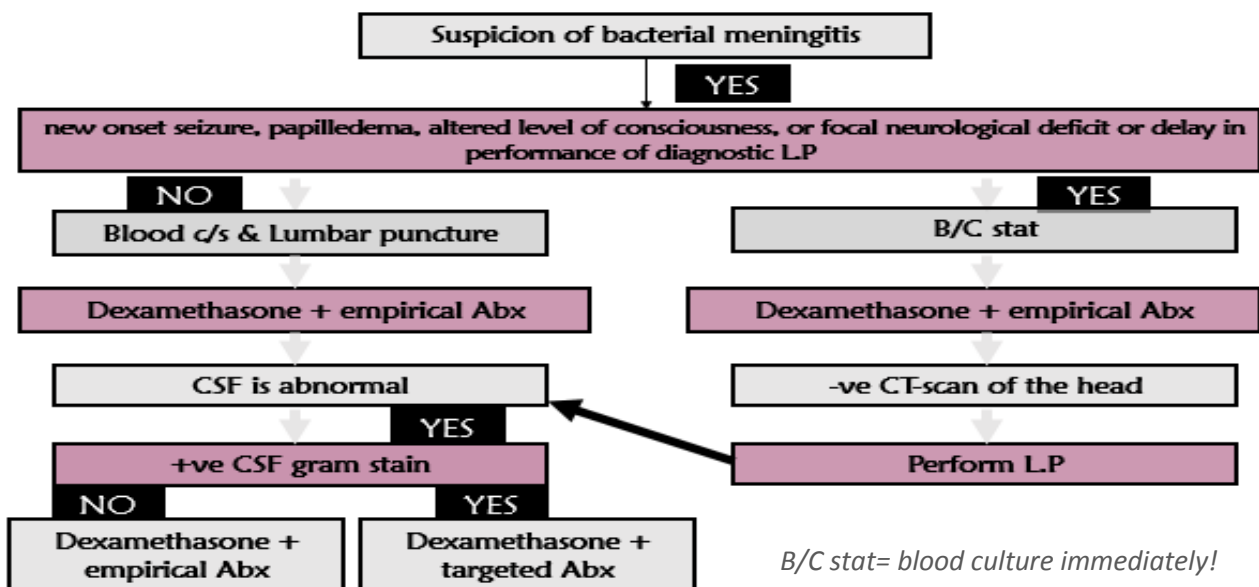
- When suspecting acute bacterial meningitis must start **empirical** treatment immediately, *even before the results of lumbar puncture and CSF are known.*
- When gram stain result is negative (cause is still undetermined) empirical treatment should be initiated with **ALL** of the following drugs administered:

- **Ceftriaxone** 2gm IV Q12h (high CFS levels)
- **Vancomycin** 500-750mg IV Q6h (**highly penicillin resistant pneumococcus**)
- **Dexamethasone** (0.15mg/kg IV Q6h) for 2-4 days:
1st dose 15-20 **min prior to or concomitant** with 1st dose of antibiotics to block TNF production
- +/- Ampicillin (for Listeria) *not always required*
- DON'T forget to give them in **MENINGEAL doses** *higher doses and more frequent doses to be able to penetrate and concentrate in CSF.*

***Role of corticosteroids** (dexamethasone) their adjunctive use prior to 1st dose of Abx are now recognized as a standard of care in the initial treatment of suspected bacterial meningitis by reducing host inflammatory response CS decrease the risk of neurological deficits sequelae caused by TNF production, and reduce morbidity and mortality rates from meningitis.

- **Management algorithm for adults: IMP!**

Management Algorithm for Adults



• Vaccination

- Vaccinate all adults >65 year old for *S. pneumoniae*
- Vaccinate asplenic patients for *S. pneumoniae*, *N. meningitidis*, and *H. influenza*
Splenectomy and asplenia result in a substantially increased risk of bacterial infection with encapsulated bacteria such as S pneumoniae, Haemophilus influenzae and N meningitidis, which are all possible causes of meningitis.
- Vaccinate immunocompromised patients for meningococcus
- Meningococcal vaccine:
 - Conjugate meningococcal vaccine: A. C. Y, W135 (menactra)
 - Effective is up to 3 years
- Pneumococcal vaccine:
 - Conjugate pneumococcal vaccine: given to children, has 7 serotypes
 - Pneumococcal polysaccharide vaccine: recommended for specific groups (old>65, adults with long term health problems, a splenic...), has 23 serotypes.

• Chemoprophylaxis

- Chemoprophylaxis with rifampicin or ciprofloxacin or ceftriaxone is recommended to prevent secondary cases in people who have been in close prolonged contact. The aim of chemoprophylaxis is to reduce the risk of invasive disease by eradicating throat carriage in those at highest risk.

II. Encephalitis

- Inflammation of the brain parenchyma
- Mostly **viral** in origin, most common organisms are:
 - ✓ Herpes simplex (HSV-1): diagnosis → PCR Treatment → high dose of Acyclovir for 3 weeks
 - ✓ Arboviruses e.g. Dengue (*a lot in Jeddah and Mecca*)
 - ✓ Rabies (*a rare fatal cause*)
- Diagnosed by CSF PCR (*the most specific and sensitive test for viral encephalitis*)
- Treatment: *supportive care + antiviral drugs + management of possible complications*

III. Brain abscess

- Organisms:
 - ✓ Streptococci (60-70%)
 - ✓ Bacteroides (20-40%)
 - ✓ Enterobacteriaceae (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

IV. Subdural Empyema

- In adults 60-90% are extension of:
 - ✓ Sinusitis
 - ✓ Otitis media
- **Surgical emergency:** must drain
- Abx same as brain abscess

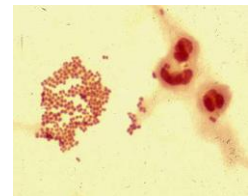
➤ CASES: IMP

Case-1:

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.

- Symptoms are suggestive of meningeal irritation
- The presence of petechiae is highly suggestive of meningococcus
- Blood culture → dexamethasone and antibiotics → CT was negative → LP → CSF results!
- **Investigations:**
 - CSF examination →
 - ✓ Opening pressure: 260 mm H2O and cloudy
 - ✓ WBC: 1500/ml: 96% polymorphs
 - ✓ Glucose: 24 mg/dl
 - ✓ Protein: 200 mg
 - Gram stain → gram-negative diplococcus (Neisseria meningitidis- meningococcus)
- **Prevention:**
 - Conjugate meningococcal vaccine: A, C, Y, W135 (menactra)
 - Up to 3 years in adult: doesn't affect nasopharyngeal carriage and doesn't provide herd immunity
- **Meningococcus:**
 - Fulminate meningococcemia with purpura → overwhelming sepsis, DIC
 - Meningitis with rash (petechiae)
 - Meningitis without rash
 - Total mortality of 3-10%
- **Treatment & chemoprophylaxis:**
 - Droplet isolation: for **48h** post Abx (*for any person with meningococcal meningitis*)
There are 4 types of transmission-based isolation:
 1. Droplet isolation → Patient is placed in a private room + Healthcare personnel wear a mask
 2. Standard isolation → all patients includes washing hands before touching/after...etc.
 3. Contact isolation
 4. Airborne isolation
 - Treatment: Ceftriaxone **7 days**
 - Chemoprophylaxis: eradicate nasopharyngeal carriage in: (*quickly before they develop meningitis*)
 - ✓ house hold contact
 - ✓ Health care providers who examined patient closely

By the following drugs → **Rifampin** 600 mg for 2 days or **Ciprofloxacin** 500mg once or **Ceftriaxone** 125 mg I.M once



- *Meningitis belt: An area in sub-Saharan Africa that has N. meningitidis as pandemic throughout the year (so if you see someone especially from Sudan who presents with meningitis immediately think of N. meningitidis)*
- *Hajj: due to an international outbreak of meningococcus following hajj in 1987 All pilgrims travelling to Saudi Arabia for the Hajj or Umrah are required to show proof of vaccination.*
- *In 2000, an international outbreak of meningococcal infection due to serogroup W135 was associated with the Hajj pilgrimage*
- *Current quadrivalent conjugate vaccines covers 4 serial groups (A, C, Y, W135) and it's good for 3-5 years*
- *Vaccine against the new serial group B is still in being developed*

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.

- A contiguous or distant focus of pneumococcal infection, such as pneumonia or otitis media → suggest *S. pneumoniae*
- **Investigations:**
 - CSF examination →
 - ✓ WBC: 3000; 99% PMN
 - ✓ Sugar: zero
 - ✓ Protein: 260 mg/dl
 - Gram stain → gram positive diplococci (*S. pneumoniae* – pneumococcal)
- **Epidemiological features of pneumococcal meningitis:**
 - The most common cause
 - Highest mortality 20-30% (*most deadly worse than N. meningitidis*)
 - 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*:**
 - Ceftriaxone 14 days (*if minimal inhibitory concentration is low*)
 - Vancomycin if Highly penicillin resistance (*if MIC is high*)
 - Steroids (pre Abx)
 - Vaccination: Pneumococcal conjugate vaccine, Pneumococcal polysaccharide vaccine



Case-3:

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
 - ✓ trans placental /vertical
 - ✓ Cross contamination(nursery)
 - ✓ inoculation(skin) farmers
 - ✓ colo/sigmoidoscopy → bacteremia / meningitis (up to 5% healthy :N flora)
- ***Listeria Monocytogenes meningitis treatment:***
 - Ampicillin 2gm IV Q4h
 - 21 day duration (3 weeks)



Case-4:

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 38.2 C, speaking well. He had ophthalmoplegia, neck stiffness and bilateral papilledema

- *Low grade fever + night sweats for 6 weeks (more chronic presentation) → suggest TB*
- Investigations:
 - CFS examination →
 - ✓ Xanthochromic (*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, Pyrazinamide, pass freely into the CSF
 - ✓ Rif 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

Case-5:

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

- *Sheep herders and farmers (animal contact) + 3 weeks (more chronic) → suggest Brucella*
- Investigations:
 - CSF examination →
 - ✓ CSF pleocytosis 105 mostly lymphocytes
 - ✓ Brucella PCR in CSF positive
 - ✓ Brucella titre 1:320
 - Blood culture → grew brucella species
- Treatment:
 - Doxycycline, Rifampin, TMP-SMX

Case-6:

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

- *From history of AVR you can suspect that it could be secondary to infective endocarditis → particularly staphylococcal infection*
- **Investigations:**
 - Blood culture → Staphylococcus Aureus
 - TEE → vegetation aortic valve
- **Treatment:**
 - Drainage of brain abscess: shows Staph. Aureus
 - Treatment: Cloxacillin, flagyl

MCQs

1. A 20 year old male, college student presents with 6 hour history of progressive headache, lethargy, nausea, and vomiting. On examination, he has temperature of 39 C and is difficult to arouse. His neck was stiff and he has left 6th nerve palsy. Rest of the examinations were normal. Because of his fever, two sets of blood cultures have been drawn, appropriate immediate further management for this patient would be:
 - A. Head CT scan and lumbar puncture (if not contraindicated by the CT result)
 - B. Lumbar puncture and laboratory evaluations followed by intravenous ampicillin
 - C. Intravenous cefotaxime or ceftriaxone followed by CT scan and lumbar puncture (if not contraindicated by the CT result)
 - D. Admit for observation after head CT scan and lumbar puncture (if not contraindicated by CT result) with antibiotics deferred pending PSF examination
 - E. Head CT scan and lumbar puncture followed by intravenous cefotaxime
2. Most common cause of encephalitis is:
 - A. HSV-1
 - B. HSV-2
 - C. Mumps virus
 - D. CMV
3. Most common cause of meningitis in adults is:
 - A. Neisseria meningitides
 - B. Subarachnoid hemorrhage
 - C. Mycobacterium tuberculosis
 - D. Streptococcus pneumoniae
4. A 19 year old female student reports general malaise, headache, and fever of acute onset. On examination at her parents' home, she is found to have mild neck stiffness, some photophobia, and a temperature of 38.1°C. What further examination is most likely to alert you to a diagnosis of **meningococcal** infection?
 - A. Testing for Brudzinski's sign
 - B. Testing for Kernig's sign
 - C. Examination of the optic fundi for evidence of raised intracranial pressure
 - D. Examination of the skin for a petechial rash
5. The husband of a patient with confirmed meningococcal meningitis is a patient in your practice. He phones to ask whether he needs prophylactic treatment. Which one of the following statements is correct?
 - A. He shouldn't receive any prophylactic treatment
 - B. He should receive prophylactic rifampicin or ciprofloxacin
 - C. Vaccination will protect him against all strains of N. meningitidis
 - D. Because of his close contact, his risk of developing meningococcal infection is high
6. Mr. Jones is a 72 year old widower who lives alone. You are asked to see him on a home visit. Unusually he has not been out today and says he has had fever and severe headache since morning. He saw your colleague at the surgery a week ago with otitis media. Examination is difficult as Mr. Jones is confused and agitated. There is purulent discharge from his ear and you are unable to visualize the tympanic membrane. He is febrile and has neck stiffness. You note that there are no rashes. You arrange urgent transport to hospital for further assessment. What organism is most likely to be causing Mr. Jones's symptoms?
 - A. Streptococcus pneumoniae
 - B. Staphylococcus aureus
 - C. Neisseria meningitidis
 - D. Mycobacterium tuberculosis

7. A 45 year old mechanical engineer from Uganda attends your surgery accompanied by his wife. They both came to the UK to live six months ago. He says he has been unwell for the past six weeks, initially with malaise and night sweats, and more recently with a severe persistent headache and vomiting. He reports weight loss of 4 kg. He has no respiratory symptoms. Which one of the following diagnoses would best fit this presentation?
- A. Meningococcal meningitis
 - B. Viral meningitis
 - C. Tuberculosis meningitis
 - D. Cerebral malaria

Answer Key:

- 1. Answer is **C** → go back to bacterial meningitis management algorithm for adults!
- 2. Answer is **A**
- 3. Answer is **D**
- 4. Answer is **D** → Presence of a petechial rash in such a patient would suggest meningococcal meningitis.
- 5. Answer is **B** → Rifampicin or ciprofloxacin are required to clear his throat carriage of *N. meningitidis* (Chemoprophylaxis)
- 6. Answer is **A** → *S pneumoniae* is the most common cause of bacterial meningitis in elderly. Patients often have a contiguous or distant focus of pneumococcal infection, such as pneumonia, otitis media, mastoiditis, & sinusitis.
- 7. Answer is **C** → Tuberculosis meningitis has a chronic presentation. An insidious prodrome followed by a meningitis phase is typical of tuberculosis meningitis.