# *CNS infections*

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***429 medicine team***

## Intro

- 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:
  - Etiology (organism)
  - Time of starting the appropriate therapy : delayed therapy causes a bad outcome
  - Use of steroids

### Definitions:

- Meningitis – inflammation of the meninges
  - The meninges are Pia, Arachnoid and Dura
- Encephalitis – infection of the brain parenchyma
- Meningoencephalitis – inflammation of brain + meninges
- Aseptic meningitis – inflammation of meninges with sterile CSF
  - Negative CSF culture

## Meningitis:

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

### Causes:

- Infectious causes:
  - Viral
  - Bacterial
  - Mycobacterium
  - Fungal
  - Brucella
- Non infectious causes:
  - Medications
  - SLE
  - Malignancy
  - Sarcoidosis
  - Aseptic meningitis
  - Behcet's disease

### Can be classified into:

- Acute: hours to days and usually bacterial or viral
- Chronic: weeks to months and usually caused by mycobacterium (TB), fungus, Lyme disease or parasites

### Types of meningitis:

#### Bacterial meningitis:

- Medical emergency of the first degree
- Common organisms:
  - Neonates:
    - Group B Streptococci 49%: because it is found in the birth canal
    - E coli, enterococci, Klebsiella, Enterobacteria, Salmonella, Serratia, Listeria

- Older infants and children: Neisseria meningitides, S. pneumoniae, M. tuberculosis, H. influenza
- Adults (IMP):
  - Streptococcus pneumonia 37%
  - Neisseria meningitides 13%
  - Listeria monocytogenes 10%
  - Other strep. species 7%
  - Gram negative 4%
  - Haemophillus influenza 4%
  - TB, Brucella
- Immuno-compromised: Listeria, gram negative bacilli, S. pneumonia

## Aseptic meningitis:

- Associated with better prognosis; self limiting and requires supportive care only
- It is an inflammation of the meninges with sterile CSF
  - CSF characteristics:
    - Negative culture IMP
    - Normal glucose and protein
    - <1000 WBC, mostly lymphocyte pleocytosis and monocytes
- Causes:
  - Enterovirus: most common cause 80% IMP
  - Partially treated meningitis due to bacteria IMP
  - HSV-2, and other viruses
  - HIV
  - Drugs: MTZ, TMP-SMX, NSAIDs, carbamazapine, IVIG (intravenous immunoglobulin)

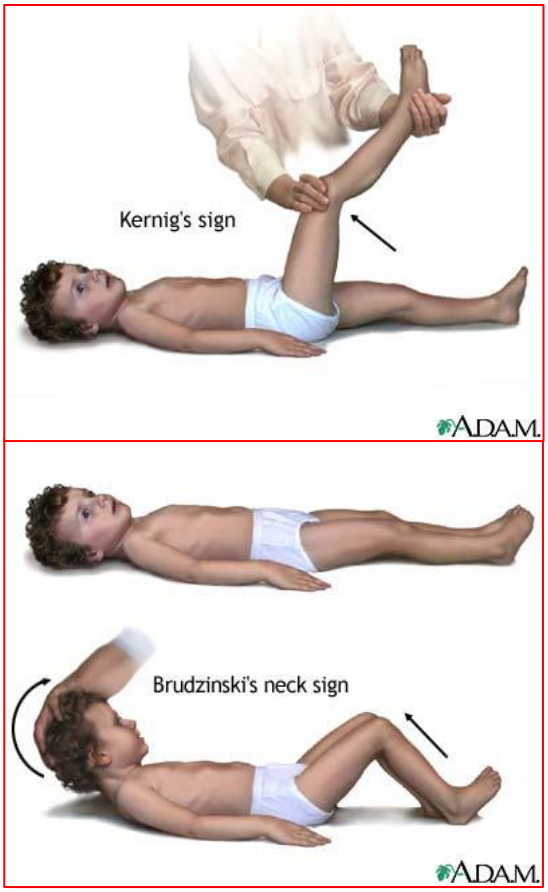
## Pathogenesis:

- Usually extends from the agents that colonize in the nasopharynx and respiratory tract, and they usually enter through:
  - Bloodstream
  - Retrograde transport through nerves
  - Contiguous spread from sinusitis, otitis media, surgery or trauma

## Clinical features of bacterial meningitis:

- Symptoms:
  - Triad of: headache, neck stiffness, and fever.
    - Usually ***HIGH GRADE SUDDEN FEVER*** in bacterial meningitis
    - Low grade fever in case of TB and Brucella and more chronic
    - Absence of this triad virtually excludes bacterial meningitis from the diagnosis
  - Altered level consciousness
  - irritability
  - photophobia
  - Vomiting
  - Seizures
  - Bulging fontanels in infants
- Signs:
  - Nuchal rigidity: stiff neck with resistance to flexion of the spine
  - Increased intracranial pressure: causing papilledema and seizures
  - Rashes
    - Maculopapular rash with petechiae

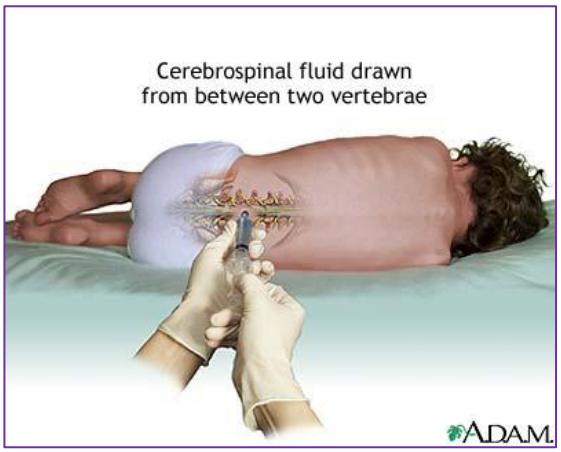
        - Petechiae and echymosis are common with meningococcal infection
        - purpura is classic for N. meningitides
    - Vesicular lesions in varicella or HSV
- Special signs:
    - Kerning's sign: while patient is lying supine, with the hip and knee flexed to 90 degrees pain limits passive extension of the knee
    - Brudzinski's sign: flexion of the neck causes involuntary flexion of the knee and hip
    - Both are found in only 50% of patients but **very specific**
- ***Most useful sign is 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
- Don't forget examining possible sources like ears, sinuses and chest... etc




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

## Investigations:

- ***CSF examination***:
    - **The most important**
    - Done through LP (lumbar puncture), contraindications:
        - ↑ ICP may increase risk of herniation
        - Cellulitis at area of lumbar puncture
        - Bleeding disorder
    - Examine the fluid (CSF appearance)
        - cloudy is consistent with pyogenic leukocytosis
    - Note the opening pressure
    - Cell count with differential – to check the percentage of polymorphs
    - Glucose, protein
    - ***Gram stain*** IMP
    - ***Culture*** IMP
    - Special tests:



- TB AFB smear PCR and culture
- Brucella serology and PCR
- HSV PCR
- Cryptococcus antigen in HIV patients

- CBC, Creatinine , electrolytes: Na
- Blood Culture IMP! Can figure out the aetiology in 20-30% of time without LP
- CXR
- CT Head

## How to differentiate between different CSF results:

- In case of suspicion of bacterial meningitis:
  - If the gram stain is positive then it is bacterial
  - If the gram stain is negative the one of the following can help you in determining if it is bacterial meningitis:

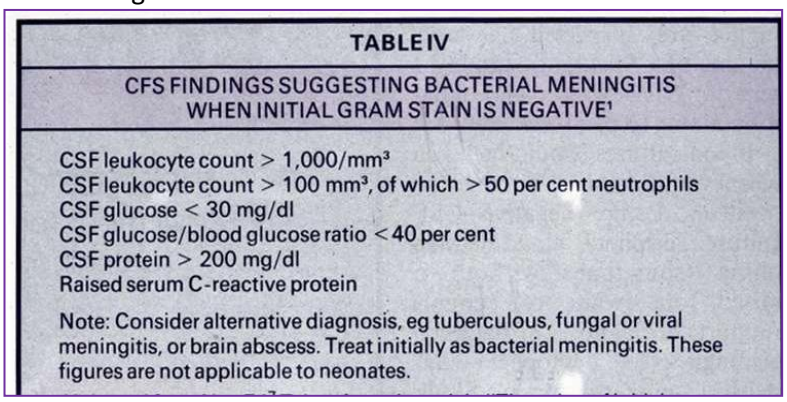


**TABLE IV**

**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.

**To differentiate between all the types:**

| | normal | Aseptic | Pyogenic (bacterial) | Tuberculosis |
|---|---|---|---|---|
| Appearance | Crystal clear | Clear/turbid | Turbid/purulent(cloudy) | Turbid/viscous |
| WBC count | <5 | 100-1000 | >1,000 (500-10000) | 50-500 |
| Differential | nil | Lymphocytes & monocytes | Polymorphs | Monocytes or lymphocytes |
| Glucose | 50-75 | Normal | <40 (low) | <30 (low) |
| Protein | <60 | >100 (moderately high) | >150 (high) | >150 (high) |

## Prevention:

- Generally:
  - Vaccinate all adults >65 year old for S.pneuomoniae
  - Vaccinate asplenic patients for S.pneuomoniae, N. Meningitides and H. Influenzae (organisms with capsules)
  - Vaccinate immune compromised patients for meningococcus
- Meningococcal vaccine:
  - Conjugate meningococcal vaccine: A, C, Y, W135 (menactra)
  - Effective Up to 3 years in adult: Does not affect nasopharyngeal carriage and does not provide herd immunity
- S.pneuomoniae vaccine:
  - Pneumococcal conjugate vaccine: gives long lasting immunity so given to children and has7 serotypes

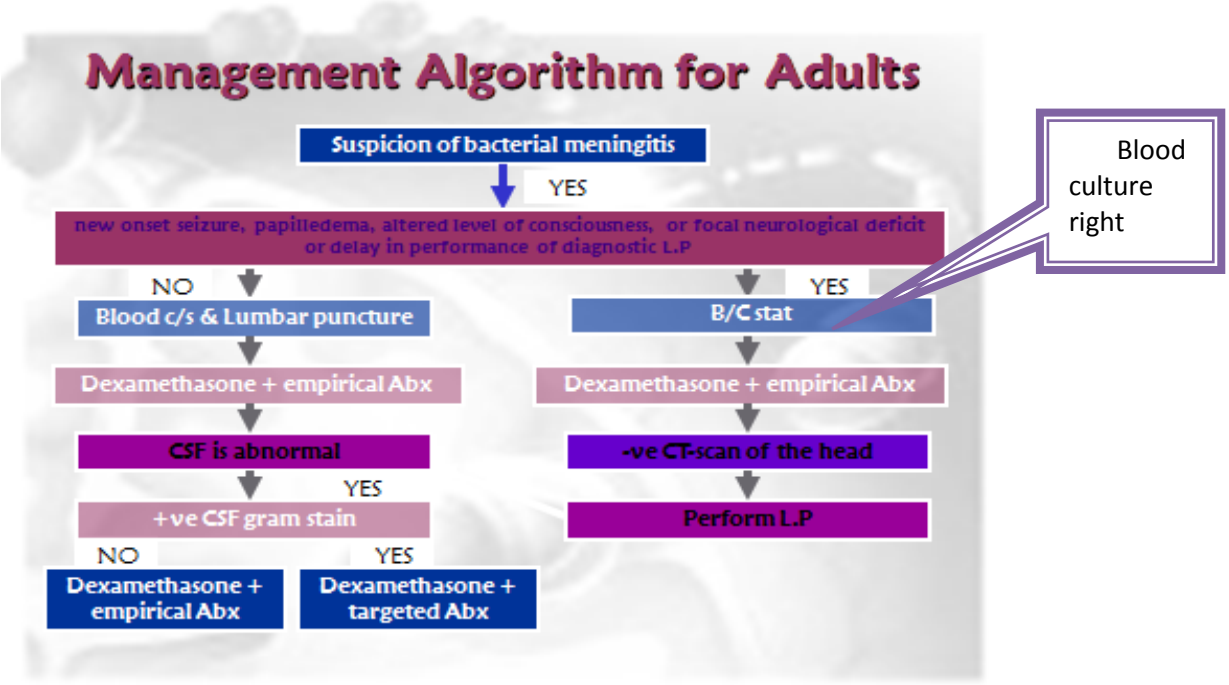
- Pneumococcal polysaccharide vaccine: recommended for special patients(old(over 65), asthmatic, diabetic, asplenic, etc..) and has 23 serotypes

## Important points to keep in mind:

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

## How to approach the patient:

- When suspecting acute bacterial meningitis you should start empirical treatment:
  - Empirical treatment when gram stain is negative (we don't know the cause) ***give ALL of the following***:
    - **Ceftriaxone** 2gm IV Q12h
    - **Vancomycin** 500-750mg IV Q6h
    - **Dexamethasone** (0.15mg/kg IV Q6h) for 2-4 days, The role of steroids in treating meningitis:
      - 1st dose 15-20 min prior to or concomitant ***with 1st dose Abx*** to block TNF production
      - Reduces inflammation and showed great beneficial **reduction on morbidity and mortality** (check the last page)
      - Decreases the risks of getting neurological deficits up to 40%
    - +/- Ampicillin (for Listeria and neonates)
  - Remember to give them in ***meningeal doses***: very high that are able to penetrate and concentrate in CSF
  - Management algorithm:

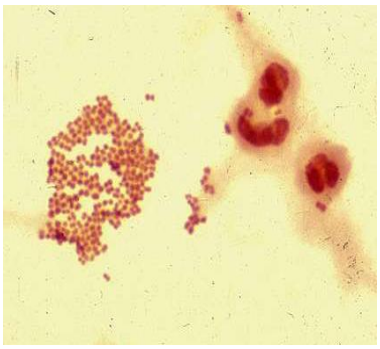



## Cases:

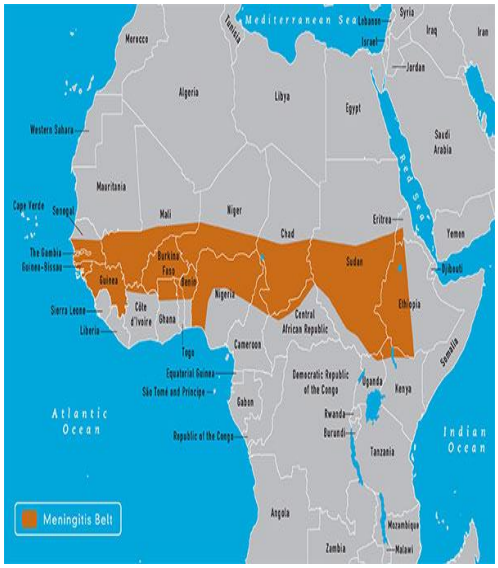
***The cases are very important; they contain the common organisms' presentations and management***

## Case 1:

- 34 years old man returning from Hajj presents with Fever, severe headache, neck stiffness, vomiting for two days, Found confused by family: ER, Temp 38.4, HR 110, BP 100/70, Obtunded, Nuchal rigidity, Kerning's and Brudzinski's signs were positive, Petechiae and echymosis on his foot
  - Symptoms suggest meningeal irritation
  - The presence of petechiae is highly suggestive of meningococcus



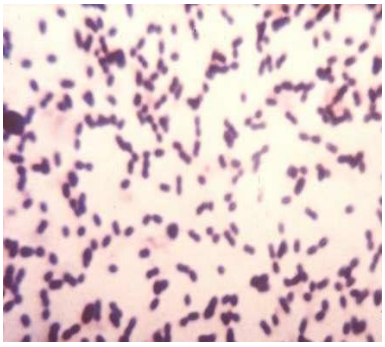
- Investigations:
  - CSF examination:
    i. Opening pressure: 260 mm H20 & cloudy
    ii. WBC: 1500/ ml: 96% polymorphs
    iii. Glucose: 24mg / dl
    iv. Protein: 200 mg
  - Gram stain: gram-negative diplococcic: Neisseria meningitides(meningococcus)
- Patients that come from areas like Sudan that lie in the meningitis belt commonly present with Neisseria meningitides




- Prevention:
  - Remember that patients from the belt should be vaccinated
  - An outbreak in 1987 in hajj made it mandatory for all people going to hajj to be vaccinated to strains: A, C, Y, W135 (menactra)
  - W135 is a recent strain that lead to an outbreak in 2000 IMP!
- Meningococcal infection has a total mortality of 3-10 % and could be :
  - Fulminate meningococcemia with purpura: Overwhelming sepsis, DIC
  - Meningitis with rash (Petechiae)
  - Meningitis without rash
- Treatment of N. meningitides:
  - Droplet isolation:
    i. Wear a mask
    ii. Put them in a private room
    iii. Leave isolation after 48 hours post ABx
  - Treatment: Ceftriaxone 7-10 days
  - Chemoprophylaxis:
    i. Rifampin 600 mg for 2 days or Ciprofloxacin 500mg once or Ceftriaxone 125mg I.M once
    ii. Eradicate nasopharyngeal carriage in contacts:
      1. house hold contact
      2. Health care providers who examined patient closely

## Case 2:

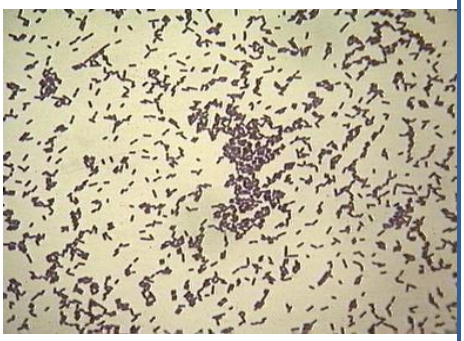
- 26 year old Saudi female presents with fever, cough and headache for the last 3 days. Examination revealed ill – looking woman with sign of consolidation over lower lungs. CXR revealed lower lobe pneumonia. Six hours after admission, her headache became worse and rapidly became obtunded.
- Investigations:
  - CSF examination:
    i. WBC: 3000 : 99% PML
    ii. Sugar: Zero
    iii. Protein: 260 mg/dl.
  - Gram stain: Gram positive diploccoci: pneumococcal (S. pneumonia)



- Pneumococcal infection features:
  - ***The most common Cause***
  - Highest mortality20 – 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 & prevention of Pneumococcus meningitis:
  - Ceftriaxone 14 days
  - Vancomycin if Highly penicillin resistance
  - Steroids (pre Abx)
  - Vaccination (mentioned earlier)

## Case 3:

- 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 week. Fever, chills and headache for 3 days. Double vision for 2 days, Neck stiffness, jolt accentuation, 6$^{th}$ CN palsy.
  - 6$^{th}$ nerve palsy and double vision indicate infection in the brainstem which is a feature of Listeria infection IMP
- Investigations:
  - CSF examination:
    i. Cloudy
    ii. WBC: 1000 70% lymphocytes
    iii. Glucose: 50mg / dl
    iv. Protein: 170 mg
  - Gram stain: Gram positive bacilli: Listeria monocytogenes



- Listeria infection features:
  - Risk groups:
    i. age <1y or >50y
    ii. Alcoholics
    iii. pregnancy: up to 30%
    iv. immunocopromised 70 %
  - route of transmission:
    i. mainly food borne
    ii. transplacental /vertical
    iii. Cross contamination(nursery)
    iv. inoculation(skin) farmers
    v. colo/ sigmoidoscopy→ bacteremia / meningitis ( up to 5% healthy :N flora)

- treatment:
    i. Ampicillin 2gm IV Q4h
    ii. 21 day duration (3 week)

## Case 4:

- 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 weeks. Temperature: 38.2 C, speaking well. He had Opthalmoplegia, Neck stiffness and bilateral papilledema.
    - From the history alone you can know that the causative organism is TB (low grade fever, night sweats for 6 weeks) so it is more chronic
- Investigations:
    - CSF examination
        i. WBC: 340 Lymphocytes: 85 %
        ii. protein 1.5g (150)
        iii. sugar 25 mg
    - Acid fast stain of the CSF: if you do 1 sample the chances of getting it right is 10% so you must do when 4 serial specimens and that will give a yield of 87%
    - Culture: ***gold standard***
    - PCR: 98% specific but low sensitivity
- Treatment of TB infections:
    - Antibiotic chemotherapy
        i. INH, Pyrazinamidine, pass freely into the CSF
        ii. Rifampin has 10% the concentration as in Plasma
        iii. Streptomycin does not pass BBB in absence of inflammation.
    - Steroids:
        i. 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, Temp 38.1 and Jolt accentuation present.
    - Brucella is common in sheep herders and farmers
- Investigations:
    - CSF examination: pleocytosis 105 mostly lymphocytes
    - Blood culture grew Brucella sp
    - Brucella titer 1:320
    - Brucella PCR in CSF positive
- Treatment: Doxycycline, Rifampin, TMP-SMX

## Case 6:

- 46 gentlemen 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 the history you can know it is secondary to infective endocarditis
- Investigations:
    - Blood Culture: staphylococcus Aureus
    - TEE: vegetation aortic valve
    - Drainage of brain abscess: shows Staph Aureus
- Treatment: Cloxacillin, flagyl (is given because abscesses are usually because of anaerobes)

## Brain abscess:

- Organisms:
  - Streptococci (60-70%), Bacteroides (20-40%), Enterobacteriacea (25-33%), S. Aureus (10-15%), S. Milleri.
  - Rare: Nocardia, Listeria
- CT brain: If abscess more than 2.5cm then surgical drainage. And if patient neurologically unstable or decrease LOC drain regardless of size
- Antimicrobials:
  - empirically Ceftriaxone with metronidazole,
  - otherwise according to susceptibility
  - Duration until response by nueroimaging

## Subdural empyema:

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

## Encephalitis

- Inflammation of the brain parnychema and often seen with meningitis, usually viral in origin.
- most common organisms are:
  - Herpes simplex: PCR, Acyclovir
  - Arboviruses e.g. Dengue
  - Rabies
- Diagnosed by CSF PCR
- Treatment: supportive care + antiviral drugs + management of complications

## Role of steroids

Experimental studies have suggested that the morbidity and mortality associated with acute bacterial meningitis results from the detrimental effects of the host inflammatory response

Treatment or modulation of host inflammatory responses during meningitis has evolved as therapeutic targets and adjunctive use of corticosteroids now are recognized as a standard of care in the initial treatment of suspected cases of bacterial meningitis in adults

1. Decreases the risks of getting neurological deficits up to 40%
2. corticosteroids have been shown to improve functional outcome and reduce mortality only in cases of acute pneumococcal meningitis
3. Adjunctive use of corticosteroids (dexamethasone 10 mg administered with the first dose of antibiotic) should begin promptly in cases of suspected bacterial meningitis and should continue at 6-hour intervals for 4 days only when S. pneumoniae infection has been confirmed.