Acute Bacterial meningitis

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OBJECTIVE

To KNOW at the end of the presentation

- Epidemiology of meningitis
- The most common organisms leading to bacterial meningitis
- Pathogenesis and risk factors of ABM
- Clinical presentation at the different ages
- Diagnosis including newer diagnostic methods
- Other investigations
- Principles of Antibiotic therapy
- Role of Adjunct therapy
- Complications
- Outcome
- Care for contacts
- Prevention of meningitis in the community

Impact of acute bacterial meningitis

- 1.2 million cases/yr
- 135,000 deaths/yr one of the top ten, in developing countries
- Beyond the newborn period most important are three heavily encapsulated organisms
  - **Strep Pneumo**
  - **H Influenza b**
  - **Neisseria meningitides**
  - All have a polysacharide capsule which increases virulence and also confers immunity if anitbody to capsule is present
- Pneumo 38-17/100,000 population
- HIB 31-46/100,000
- Overall death rate 31-40/100,000

Acute Bacterial Meningitis

What are the most common organisms in the different age groups?

Table 4. Bacterial Meningitis in the United States (% of Total Cases)

Age	Organisms
0-4 weeks	*Streptococcus agalactiae, Escherichia coli, Listeria monocytogenes, Klebsiella pneumoniae, Enterococcus* spp., *Salmonella* spp.
4-12 weeks	*S. agalactiae, E. coli, L. monocytogenes, Haemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitidis*
3 months to 18 years	*H. influenzae, S. pneumoniae, N. meningitidis*

Adapted from Tunkel AR, 2000.

This is also applicable to our region

Acute Bacterial Meningitis beyond the neonatal period

3 months - 6 years
- Strep Pneumo
- H flu b
- Neisseria meningitides

>6 yrs
- Strep pneumo and N meningitides

Post Head trauma
- Strep Pneumo
- H flu b.

Post Shunt, Neurosurgery
- Staphylococcus epi/aureus, gram negatives

Recent findings in meningitis

Epidemiology

- Decrease in HIB to almost nill after vaccination
- Decrease in pneumo after PCV 7 and 13 vaccines in countries that use them
- Decrease in GBS with antenatal screening and treatment. In our region ? increase
- Median age increased
- No change in CFR about 15% in the adult
- In both adults and children strep pneumo is most common, listeria common in the elderly >65 yrs

Pathogenesis

- 1. Colonisation of the nasopharynx antidates bacteremia
- 2. Viral infection of the upper respiratory tract may increase the risk of bacterial entry into the blood
- 3. BBB plays a major role in protecting the CNS, In the newborn the BBB is poorly developed. Meningitis may be present in up to 20% of sepsis

Acute bacterial meningitis

Bacterial pathogenetic factors

- Polysaccharide capsule is common to all pathogens.
  HIB, Strep pneumo, Neisseria,
- In the newborn, E coli K1 antigen, Listeria monocytogenes and Gp b Strep all have capsules.
- Anticapsular antibodies=protection

Molecular pathogenesis

- Pili by meningococcus help attach to the mucosa
- Laminin receptor for the organisms does play a role. This is inducible on endothelial surfaces and allows organisms to bind to the endothelium and enter into the CNS
- Organisms that could not bind to the laminin receptor do not cause meningitis

Recent advances in pathogenesis

Pathogenesis stage	Host defense	Pathogen strategies
Mucosal colonization and invasion	Secretary IgA Ciliary activity	IgA protease Adhesive Pili, neisseria
Blood stream survival	complement	Evasion of alternate complement pathway by polysacharide capsule, innate immunity
Cross blood brain barrier	Cerebral endothelium	Usurp laminin-R Potential role of MIF, TNF
CSF survival	Poor opsonic activity	Bacterial replication

Host factors that increase the risk for meningitis

- Extremes of Age
- Male sex
- Def of C5-8
- Def in IgM , IgG
- Asplenia, congenital or surgical
- Head trauma
- Chronic disease, Diabetes, Addison, Hypothyroid, CF
- Renal insufficiency
- Children with facial cellulitis, periorbital cellulitis, sinusitis, and septic arthritis have an increased risk of meningitis.
- Poverty
- Attendance at day care and Crowding
- mass pilgrage such as Hajj increase the risk of exposure and carraige

Neonatal meningitis

- More common in the premature
- More common with sepsis
- 0.3/1000 live births in developed countries
- HSV 0.02-0.3/1000
- 2.4/1000 in Kuwait
- Rate in Jordan still undetermined

Epidemiology in neonatal meningitis

- GBS 50% of cases
- E Coli 20%
- Listeria 5-10% may be acquired transplacentally
- In developing countries ?? GNB
- HSV acquired at birth, may get sick in the second week of life leading to meningitis or encephalitis
- Enterobacter sakazakii was reported following ingestion of contaminated reconstituted formula
- Enteroviruses may cause up to 3% of cases with sepsis and meningitis

Pathophysiology

- Colonization from the mother such as GBS
- <32 weeks little immuneglobulin
- Inefficiency of the complement alternate pathway less defense for encapsulated bacterial
- T and B cell function compromised
- Deficient migration and phagocytosis
- Poor BBB

Neonatal meningitis common organisms

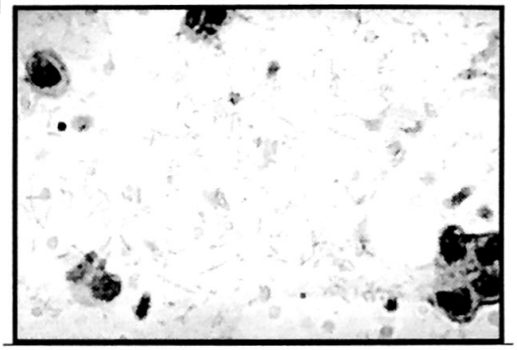
- Early onset<3-7 days,
  - GBS,E Coli, Listeria, enteroviruses
- Late onset >7 days
  - GBS, E Coli, Other GNR, Listeria
  - Staph, Enterococcus, Candida, HSV, Enteroviruses

Prognosis in the newborn

- Death 10% in bacterial meningitis and 15% in HSV
- HSV 1 and 2 same mortality
- Morbidity with increased CP,MR, Seizures,microcephaly
- 5-20% epilepsy
- 25-50% significant problems with language, motor function or cognition
- Poor indicators include LBW, significant leukopenia or neutropenia, High CSF protein
- Delayed sterilizaiton of the CSF and coma
- Seizures lasting longer than 72 hours or hypotension needing inotropes predict moderate to severe disability or death
- MRI must be done on all neonates following meningitis

Acute Bacterial Meningitis

What is the epidemiology of the different pathogens after the neonatal period?

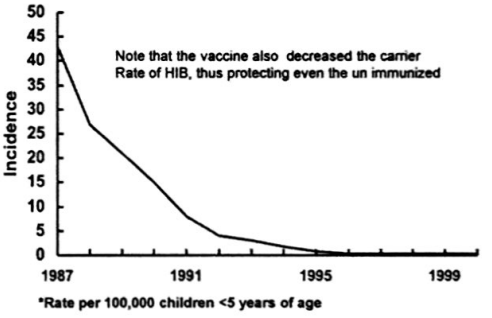


Acute Bacterial Meningitis

H Flu B

- serotype a-f
- Polyshaccharide capsule determines serotype and pathogenecity,
- only b causes major invasive disease
- Anticapsular antibodies are protective
- Organism is acquired from the respiratory tract by droplet,NP carraige of HIB is uncommon 4%
- NP, Nontypable 80%
- newborn is protected by maternal antibodies
- till age 2-3 months, young<4 years contacts are at high risk ,HIB Vaccination almost eradicated the disease

Estimated Incidence* of Invasive Hib Disease, 1987-2000



Streptococcus pneumoniae

- 90 different serotypes
- Capsule is principle virulence factor
- Antibodies against capsule = protection
- Each serotype in vaccine = antibody
- Limited serotypes cause majority infections
- 14,6B,19F,18C,23F,4,9V = 80% infections
- PCV7 licensed in 2/2000
- 2,4,6 and 12 -15 mos, high risk 24 - 59 mos

Strep pneumo

- Carrier state not uncommon
- No increased risk to contacts
- Disease more common in certain hosts
  - Sickle cell patients (functional asplenia)
  - Nephrotic syndrome
  - Asplenia
  - IgG def
  - Properdin deficiency
  - Most common cause of meningitis with basal skull fracture

Acute bacterial meningitis

Neisseria meningitides

- Serotypes, a,b,c,x,y,z,29E,W135
- Anticapsular antibody=protection
- A in Africa and the ME
- B,C in the USA, Europe
- Outbreaks Q 7-10 yrs
- Infants 6-12 months and adolescents are at high risk especially in dry season,and following URI
- Recent Hajj Outbreaks with W135.

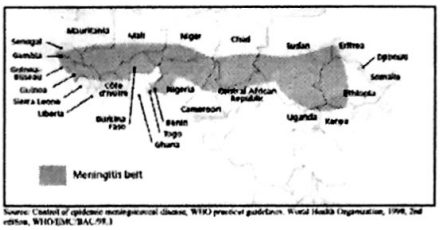


Figure 1. The African meningitis belt. Those sub-Saharan countries are at high epidemic risk for meningococcal meningitis.

Acute bacterial meningitis

- Neisseria Meningitides
- Carrier rate 1-15%. Interepidemic 3%
- Family contacts 40-50%
- Risk of disease in contacts 1%
- Pts with C5-C8 def, have very bad disease
- Early colonization with Neisseria lactamicus seems to be protective

Listeria monocytogenes

- Most common in the newborn and older than 50 years of age
- Serotype 1a,1b and 1Vb most common
- May affect the immune compromised and pregnant women as well
- May be associated with consumption of raw milk and unpasteurized cheese.
- Signs and symptoms may be subtle and low grade, the diagnosis may be delayed.
- ~~Misidentified as diphtheroid and alpha strep~~

Prognostic factors, poor prognostic factors

- High Bacterial load> 10^7/ml
- Age, Neonatal mortality 15-20%, infants 2-5%
- Seizures after 4th day of admission
- Focal neurological deficit
- Deteriorating level of consciousness
- Hypotension and coma at admission
- S pneumo has the worst prognosis
- Inappropiate ADH release
- Delayed sterilization of the CSF, this should occur after 24 hours of therapy in children and < 4 days in the newborn
- Developing countries worse outcome

How do we diagnose meningitis

- Classically fever, headache, stiff neck and positive meningeal signs are present
- Clinical presentation depends on age and Classical signs may be absent at extremes of age,
- However changes in mental status expecially headache are present.
- In the infant paradoxical irritability may be present
- Bulged fontanelle is a late sign
- Must maintain a high sense of suspicion

Table 1. Common Presenting Symptoms and Signs in Children (<14 years old) with Bacterial Meningitis

Symptom/Sign	Relative Frequency (%)
Fever	85-99
Irritability	34-65
Meningismus	67-96
Altered sensorium/comatose	7-12
Kernig's sign	N/A
Brudzinski's sign	N/A
Vomiting	18-59
Seizure	11-30
Focal findings	7

Adapted from Kaplan SL, 1999.

Diagnosis of ABM

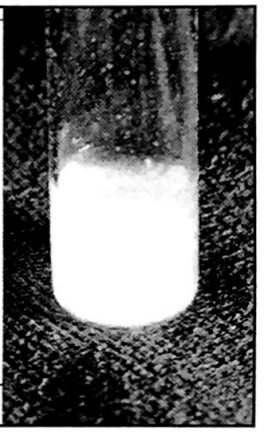
- CSF examination is a must
- Other tests are only adjunct BUT cannot be diagnostic
- However in patients who are very ill or if it is not possible to perform an LP it is acceptable to start treatment with antibiotics
- The CSF will remain abnormal for several days afterwards and can make the diagnosis.

GUIDELINES FOR CT SCAN OF HEAD PRIOR TO LUMBAR PUNCTURE (B-II)

- ALL Patients must have an eye examination for papilledema
- CT SCAN or MRI must be done if
  - Age is older than 60 years
  - Patient has Immunocompromised state
  - Patient has New onset seizure
  - Patient has Altered consciousness
  - Patient has Papilledema
  - Patient has Focal neurologic deficit

CSF testing

- Cell count and diff
- Glucose and Protein
- Culture and gm stain
- ?? Other tests such as
- Latex agglutination, PCR



CSF FINDINGS IN BACTERIAL MENINGITIS (classical findings)

CSF Parameter	Typical Findings
Opening pressure	200-500 mm H_2O
White blood cell count	1000-5000/mm^3
Percentage of neutrophils	≥80%
Protein	100-500 mg/dL
Glucose	<40 mg/dL
CSF:serum glucose	≤0.4

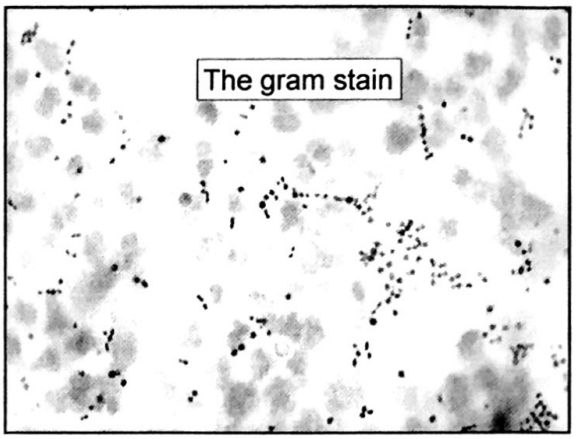
Note of caution

- The total WBC count cannot definitely distinguish between bacterial and other causes.
- At one time, it was generally believed that a predominance of polymorphonuclear leukocytes (PMNs) pointed to bacterial meningitis, but this has been an unreliable indicator; bacterial meningitis may also present with a lymphocytic predominance.
- Attempts to differentiate bacterial and aseptic meningitis on the basis of percentage and absolute number of premature neutrophils (ie, bands) have not yielded diagnostic results.[15]

  - Kanegaye JT, Nigrovic LE, Malley R, Cannavino CR, Schwab SH, Bennett JE, et al. Diagnostic value of immature neutrophils (bands) in the cerebrospinal fluid of children with cerebrospinal fluid pleocytosis. *Pediatrics*. Jun 2009;123(6):e967-71. [Medline].

CSF analysis, important considerations A cautionary note, IDSA guidelines

- Both *N meningitidis* meningitis and *S pneumoniae* meningitis are known to give normal CSF results. In an evidence-based article, meningitis was found to exist in 10% of children who have normal CSF analysis.
- Several gram-negative bacteria and higher serotypes of *S pneumoniae* have capsular antigens that cross-react with *H influenzae* type b polyribophosphate.
- Capsular antigens of group B meningococcus cross-react with K1-containing *Escherichia coli*. Gram stains of CSF are more sensitive than these rapid diagnostic tests for the detection of *N meningitidis*.



CSF GRAM' S STAIN

- Identifies causative microorganism in 60-90% of cases, with a specificity of ≥97%
- Likelihood of positive Gram' s stain depends upon CSF concentration of microorganisms, specific bacterial pathogen, and prior antimicrobial therapy
- False-positive results may result from observer misinterpretation, reagent contamination, use of occluded lumbar needle (skin contamination)
- Rapid, inexpensive, highly specific (A-III)

CSF LATEX AGGLUTINATION IN CULTURE-PROVEN BACTERIAL MENINGITIS

Microorganism	Sensitivity (%)
Haemophilus influenzae type b	78-100
Neisseria meningitidis	50-93
Streptococcus pneumoniae	67-100
Streptococcus agalactia	69-100

Gray LD, Fedorko DP. Clin Microbiol Rev 1992;5:130.

1 Test. 14 Targets. All in about an hour.


Bacteria


Viruses

Bacteria	Viruses
Escherichia coli K1	Cytomegalovirus (CMV)
Haemophilus influenzae	Enterovirus
Listeria monocytogenes	Herpes simplex virus 1 (HSV-1)
Neisseria meningitidis	Herpes simplex virus 2 (HSV-2)
Streptococcus agalactiae	Human herpesvirus 6 (HHV-6)
Streptococcus pneumoniae	Human parechovirus
	Varicella zoster virus (VZV)

PCR testing now available as multiplex

Acute Bacterial Meningitis

Treatment of acute bacterial meningitis

Principles of antibiotic therapy

- Must give empiric antibiotic therapy immediately
- Must cover ALL possible pathogens no matter how small is the risk of infection
- Must choose a bactericidal agent
- Must choose an agent that crosses the CSF very well and have a good MIC against the organisms

GUIDELINES FOR TIMING OF ANTIMICROBIAL ADMINISTRATION

- "time is brain"
- First dose no later than 2 hours of contact
- If taking care of patients in a remote location and cannot obtain CSF give antibiotics BEFORE transfer
- CSF abnormality will persist for a few days
- Prior antibiotics only interfere with culture
- Hence DO NOT DELAY giving antibiotics for referral of patients

EMPIRIC ANTIMICROBIAL THERAPY OF PURULENT MENINGITIS (A-III)

Age	Antimicrobial Therapy
<1 month	Ampicillin + cefotaxime; or ampicillin + an aminoglycoside
1-23 months	Vancomycin + a third generation cephalosporin[a]
2-50 years	Vancomycin + a third generation cephalosporin[a]
Older than 50 years	Vancomycin + ampicillin + a third generation cephalosporin[a]

[a]cefotaxime or ceftriaxone IDSA guidelines

EMPIRIC ANTIMICROBIAL THERAPY OF PURULENT MENINGITIS (A-III)

Predisposing Condition	Antimicrobial Therapy
Immunocompromise	Vancomycin + ampicillin + cefepime or ceftazidime
Basilar skull fracture	Vancomycin + a third generation ceph
Head trauma or after neurosurgery, or CSF shunt	Vancomycin + either ceftazidime, cefepime, or meropenem

[a]cefotaxime or ceftriaxone

TARGETED ANTIMICROBIAL THERAPY IN BACTERIAL MENINGITIS (A-III)

Microorganism	Antimicrobial Therapy
S. pneumoniae	Vancomycin + a third generation cephalosporin[a,b]
N. meningitidis	Penicillin G, ampicillin, or a third generation ceph
L. monocytogenes	Ampicillin or penicillin G[c]

[a]cefotaxime or ceftriaxone
[b]addition of rifampin may be considered
[c]addition of an aminoglycoside may be considered

ANTIMICROBIAL THERAPY IN BACTERIAL MENINGITIS (A-II, A-III)

Organism	Antimicrobial Therapy
Streptococcus pneumoniae	
PCN MIC <0.1 μg/mL	Penicillin G or ampicillin
PCN MIC 0.1-1.0 μg/mL	Third generation cephalosporin[a]
PCN MIC ≥2.0 μg/mL	Vancomycin + a third generation cephalosporin[a]
CTX MIC ≥1.0 μg/mL	Vancomycin + a third generation cephalosporin[a]

[a]cefotaxime or ceftriaxone

ANTIMICROBIAL THERAPY IN BACTERIAL MENINGITIS (A-I, A-III)

Organism	Antimicrobial Therapy
Neisseria meningitidis	
PCN MIC <0.1 μg/mL	Penicillin G or ampicillin
PCN MIC 0.1-1.0 μg/mL	Third generation ceph[a]
Haemophilus influenzae	
β-lactamase-negative	Ampicillin
β-lactamase-positive	Third generation ceph[a]

[a]cefotaxime or ceftriaxone

ANTIMICROBIAL THERAPY IN BACTERIAL MENINGITIS (A-II, A-III)

Organism	Antimicrobial Therapy
Enterobacteriaceae ceph[a], or	Third generation meropenem
Pseudomonas aeruginosa	Ceftazidime[b], cefepime[b], or meropenem[b]
Streptococcus agalactiae	Ampicillin or penicillin G[b]
Listeria monocytogenes	Ampicillin or penicillin G[b]
Staphylococcus aureus	Nafcillin or oxacillin
MRSA or *S. epidermidis*	Vancomycin

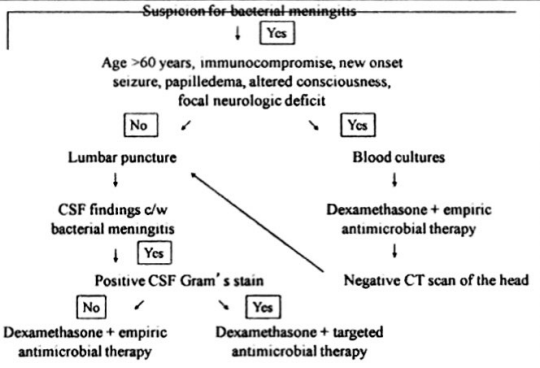
[b]addition of an aminoglycoside should be considered

ADJUNCTIVE DEXAMETHASONE RATIONALE

- The subarchnoid space inflammatory response during bacterial meningitis is a major factor contributing to morbidity and mortality
- Attenuation of this inflammatory response may diminish many of the pathophysiologic consequences of bacterial meningitis (e.g., cerebral edema, increased intracranial pressure, altered cerebral blood flow, cerebral vasculitis, neuronal injury)

The Guideline on ADJUNCTIVE DEXAMETHASONE IN BACTERIAL MENINGITIS

- Neonates (C-I) (not proved)
- Infants and children with *Haemophilus influenzae* type b meningitis (A-I)
- Infants and children with pneumococcal meningitis (B-I)
- Adults with pneumococcal meningitis (A-I)
- Patients with pneumococcal meningitis caused by highly penicillin- or cephalosporin-resistant strains (B-III)
- Administer at 0.15 mg/kg every 6 hours for 2-4 days concomitant with or just before first antimicrobial dose



Prognosis mortality

- Overall mortality for bacterial meningitis is 5-10%.
- In neonates, mortality is 15-20%, whereas in older children, it is 3-10%.
- *S pneumoniae* meningitis 26.3-30%;
- Hib meningitis 7.7-10.3%;
- *N meningitidis* has the lowest, at 3.5-10.3%.

Duration of antibiotic therapy

- *N meningitidis* 7 d
- *H influenzae* 7 d
- *S pneumoniae* 10-14 d
- *S agalactiae* (GBS) 14-21 d
- Aerobic gram-negative bacilli 21 days or 2 wks beyond the first sterile culture (whichever is longer)
- *L monocytogenes* 21 d or longer

End of therapy

- No need to repeat CSF if uncomplicated course
- Repeat CSF in the neonate and if complicated
- CT or MRI must be performed in the newborn at discharge to rule out abscess or hydrocephalous
- Brain stem evoked potential for hearing evaluation must be done for all individuals recovering from meningitis

Prevention of meningitis

- Prophylaxis should be given to contacts of cases of HIB and Meningococcal infections
- Meningococcal meningitis
  - Give to ALL household or very close contacts regardless of age
  - Risk of secondary case is 1%
  - Rifampicin, or ceftriaxone, or ciprofloxacin
  - PLUS meningococcal vaccine

Prophylaxis for H flu b

- Risk of disease is age dependent
- Secondary disease in first month is 0.3%
- 600X general population in young children
  - <2years old 3.7%
  - >6 yrs 0

Secondary cases 64%in 1st wk
20% in 2nd wk,
16% in 3rd wk.

Prophylaxis for contacts of H flu b

- Rifampin 20mg/kg/dX4 d

Give to ALL household contacts adults and children, if child <4 years of age and not vaccinated or if the child is less than one year of age

- Day care???

Prevention of infection in the community

- Conjugate polysacharide vaccines to
  - H flu b
  - Strep pneumo
  - Meningococcal vaccines

Complications

- Death 3-5%
- Subdural effusion/empyema
- Hearing deficit 7-30%
- Decreased IQ 30-50%
- Seizures
- Hemiparesis,
- Other neurological deficit

Prognostic factors in ABM
CFR (Case fatality rate)

	Developed countries	Underdeveloped
S pneumo	20%	50%
Sequelea	30%	60%
Older adults	40%	

Conclusions

- Acute bacterial meningitis remains a major cause of mortality and morbidity despite excellent antibiotics
- Host factors play a major role in brain damage, need more drugs against this
- Dexamthasone adjunct therapy now recommended for children and adults

Conclusions

- Outcome may be more guarded with subtle brain damage and decreased IQ
- Developing countries have a worse outcome with the disease
- Prevention is primary vaccines for all three pathogens are now present
- In jordan we have only introduced H flub