Acute Bacterial Meningitis beyond the Neonatal Period

Dr. Zahra pourmoghaddas

Isfahan University of Medical Sciences

PATHOGENESIS AND PATHOLOGY

Bacterial colonization of the nasopharynx or skin

Mucosal invasion (or breach in skin barrier) and penetration into the bloodstream

Intravascular multiplication and entrance through the (BBB)

Generation of inflammation within the subarachnoid space

Induction of neuronal and auditory cell damage

PATHOGENESIS AND PATHOLOGY

- **The three most common organisms causing hematogenously acquired acute bacterial meningitis worldwide :**
- **Streptococcus pneumoniae, Neisseria meningitidis, and Haemophilus influenzae type b (Hib)**

PATHOGENESIS (Hib)

- Vaccination and meningitis:
- Introduction: ۱۹۸۷
- Hib vaccination in Asia: ۲۰۰۲
- Mongolia: ۲۸/۱۰۰ ۰۰۰ children in ۲۰۰۲–۲۰۰۵ to ۲/۱۰۰ ۰۰۰ in ۲۰۰۸–۲۰۱۰
- In Pakistan: reduced Hib meningitis by ۸۹%

- https://doi.org/۱۰/۱۰۹۳٪۲Finfdis٪۲Fjiaa۵۳۷

PATHOGENESIS (Hib)

- Inroduction in Iran: ۲۰۱۴
- ۴۶/۲% decrease in the meningitis of all ages and a ۵۷% decrease in children under five
- The death rate was reduced to ۲/۱%
- ۱۰/۲۹۹۱/jegh.k.۲۱۰۳۳۰/۰۰۱

PATHOGENESIS (S.Pneumonia)

- ٢/٥ per ١٠٠,٠٠٠ before ٢٠٠٠.
- Seven of the >٩٠ pneumococcal serotypes (٤, ٦B, ٩, ١٤, ١٨F, ١٩F, and ٢٣F) accounted for >٨٠% of invasive disease in children from developed countries; serotypes ٥ and ١ also are prevalent in developing countries
- The incidence of invasive disease, including meningitis, fell by greater than ٩٠% after the implementation of conjugate vaccination (PCV٧)

Sarah S. Long, Larry K. Pickering, Charles G. Prober · ٢٠١٢ · Medical

PATHOGENESIS (S.Pneumonia)

- Increase in **invasive pneumococcal disease caused by nonvaccine serotypes ١٩ A (resistant to β-lactam antibiotics, including penicillin and third-generation cephalosporins)**
- **(PCV١٣) includes the ١٩A serotype as well as types ١ and ٥ that are more common in the developing world**

PATHOGENESIS (S.Pneumonia)

- In Iran:
- Serotypes ۳, ۲۳F, and ۱۹F : ۴۶% of invasive disease.(in Tehran)
- The ۱۳-valent pneumococcal vaccine provides the highest coverage (۶۶/۲۳%), followed by the ۱۰-valent vaccine (۳۴/۹%) and, lastly, the ۷-valent vaccine (۳۳/۷۱%)
- https://doi.org/۱۰/۵۸۱۲/ijp.۱۰۶۰۸۶

PATHOGENESIS (N.meningitis)

- Serogroups B and C are the most common serogroups : invasive infections in North America.
- Y strains can account for up to ٢٠% to ٢٥% of cases

In ٢٠٠٥, the quadri-valent meningococcal (A/C/Y/W-١٣٥) (MCV٤) was licensed and is recommended currently for all U.S. adolescents beginning at ١١ to ١٢ years of age and for persons ٢ through ٥٤ years of age who have elevated risk for invasive meningococcal disease

Sarah S. Long, Larry K. Pickering, Charles G. Prober ·٢٠١٢ ·Medical

PATHOGENESIS (N.meningitis)

- The **effectiveness** of the conjugate vaccines was ٩٩% – ١٠٠%.
- **Incidence decline** of laboratory-confirmed meningococcal disease for the conjugate vaccine ranged from ٧٧% – ١٠٠% among different ages groups.

https://doi.org/١٠.٢٦٣٣٪٢FRPSP.٢٠١٧.١٥٨

PATHOGENESIS (N.meningitis)

- MenB vaccine series among persons aged ≥١٠ years who are at increased risk for serogroup B meningococcal disease
- In Uk: at ٨ and ١٦ weeks, with a booster at ١٢-١٣ months.
- There are no plans for a catch-up programme for older children, because the main burden of the disease is in young babies, with a peak around ٥ to ٦ months of age.
- Protects against ٧٣-٨٨% of MenB strains causing invasive

- https://doi.org/١٠/١٠١٦/j.jinf.٢٠١٥/٠٩/٠٣٥
- https://www.cdc.gov/mmwr/volumes/٦٩/rr/rr٦٩٠٩a١.htm

PATHOGENESIS (N.meningitis)

- ۵۰۶ pediatric patients suspected to CNS infection from ۴ cities of Iran
- ۱۱/۵%, ۴/۸%, and ۴/۱% of *S. pneumoniae*, *H. influenzae*, and *N. meningitidis* were identified
- https://doi.org/۱۰/۱۱۵۵/۲۰۲۳/۳۵۰۲۶۶۶

CLINICAL MANIFESTATIONS

- **Symptoms and signs of bacterial meningitis depend, in part, on the age of the patient and duration of the illness.**
- **Often, clinical manifestations are nonspecific and are not readily distinguished from those of self-limited viral infection**

- Randall G. Fisher, Thomas G. Boyce, Hugh L. Moffe. ٥th edition

CLINICAL MANIFESTATIONS

- The classic symptoms of fever, headache, neck stiffness, followed by altered mental status and petechial rash, were most frequently described for adults and older children
- For children, there were a wider range of symptoms reported, with some such as leg pain and cold hands and feet
- The symptoms in infants and neonates were more general and can be un-distinguishable from sepsis
- https://doi.org/١٠/١١٨۶/s١٢٩١۶-٠١٩-١٣٨٧-۵

CLINICAL MANIFESTATIONS

- **Irritability, fever and poor feeding were most commonly described, followed by bulging fontanelle, petechial rash and lethargy.**
- **High fever can be a sign of severity, fever might not always be present particularly in neonates**
- **According to ESCMID there are no clinical signs and symptoms that are present in all children**
- https://doi.org/١٠/١١٨٦/s١٢٩١٦-٠١٩-١٣٨٧-٥

CLINICAL MANIFESTATIONS

- **The onset of acute meningitis has two predominant patterns.**
- **Most often,meningitis is preceded by several days of fever accompanied by UR symptoms or GI symptoms, followed by nonspecific signs of CNS infection, such as increasing lethargy and irritability.**
- **The more dramatic presentation is less common and presents with sudden and progressive shock, purpura, disseminated intravascular coagulation, and reduced levels of consciousness often resulting in progression to coma or death within ٢٤ hr.**

CLINICAL MANIFESTATIONS

- **As with simple testing for nuchal rigidity, Kernig and Brudzinski signs are meant to help the physician detect inflammation of the meninges.**
- **Demonstration of their clinical utility is lacking.**
- **Nuchal rigidity may not be elicited in comatose patients or when signs of focal or diffuse neurologic impairment are present.**
- Randall G. Fisher, Thomas G. Boyce, Hugh L. Moffe. 5th edition

CLINICAL MANIFESTATIONS

- **At the time of initial evaluation, ۶۰% to ۸۰% of children have a stiff neck .**
- **Meningitis in children beyond the neonatal period revealed that (۱/۵%) had no meningeal signs during their entire period of hospitalization, despite the presence of CSF pleocytosis**
- Randall G. Fisher, Thomas G. Boyce, Hugh L. Moffe. ۵th edition

CLINICAL MANIFESTATIONS

- **Bacterial meningitis cannot be ruled out based on the absence of classical signs and symptoms alone**
- https://doi.org/١٠/١١٨۶/s١٢٩١۶-٠١٩-١٣٨٧-۵

Diagnosis

- **A lumbar puncture to obtain CSF is necessary when the diagnosis of bacterial meningitis is considered**

Diagnosis

- **The Oostenbrink rule is potentially the most useful for physicians because it is simple and can guide decisions about performing a lp and about treating patients empirically with antibiotics.**
- **When originally developed, the rule stated that patients with a score of ٩/٥ or more should have a lumbar puncture**
- PMID: ١١٤٤٠٠٩١

RISK FACTOR	*POINTS*
Duration of main problem in patient history	1.0 per day (maximum 10)
History of vomiting	2.0
Physical examination findings:	
Cyanosis	6.5
Disturbed consciousness	8.0
Meningeal irritation*	7.5
Petechiae	4.0
Serum C-reactive protein level, mg per dL (mg per L)	
< 5.0 (50)	0
5.0 to 9.9 (50 to 99)	0.5
10.0 to 14.9 (100 to 149)	1.0
15.0 to 19.9 (150 to 199)	1.5
≥ 20.0 (200)	2.0
Total:	_____

Diagnosis

- KCH-٢٠٠٢ (Kilifi County Hospital ٢٠٠٢):
- The presence of ≥١ of a bulging fontanel, neck stiffness, cyanosis, impaired consciousness, partial seizures, and seizures outside the febrile convulsions age range is a clear indication for lumbar puncture and/or presumptive treatment
- https://doi.org/١٠/١٥٤٢/peds.٢٠٠٤-٠٠٠٧
- Sensitivity ٨۶%(٩٥% CI ٧٧–٩٢), specificity ٣٨% (٩٥% CI ٣٧–٣٨), NPV ١٠٠% (٩٥% CI ٩٩–١٠٠)
- https://doi.org/١٠/١١٨۶/s١٢٩١۶-٠٢١-٠١٩٩٨-٣(٢٠٢١)

Diagnosis

- **(IMCI) signs: (lethargy, impaired consciousness, convulsions, or a stiff neck)**
- **One or more IMCI signs sensitivity ٨٠% , specificity ٦٢% NPV ١٠٠%**
- **https://doi.org/١٠/١١٨٦/s١٢٩١٦-٠٢١-٠١٩٩٨-٣(٢٠٢١)**

Diagnosis

- **Before lumbar puncture is done, the optic fundi should be examined to exclude papilledema.**
- **Papilledema takes time to develop, and its absence does not rule out elevated ICP**

- Randall G. Fisher, Thomas G. Boyce, Hugh L. Moffe. 5th edition

Diagnosis

Elevated ICP : focal neurologic signs, postural or respiratory abnormalities, absent oculocephalic (doll's eyes) reflexes, dilated and unequal pupils, ophthalmoplegia, protracted seizures, and severe obtundation or coma (GCS <^)

Randall G. Fisher, Thomas G. Boyce, Hugh L. Moffe. ^5th edition

Diagnosis

- **Patients with these signs or symptoms should undergo an emergency (CT) scan prior to lumbar puncture in order to minimize the risk of cerebral herniation.**
- **If the CT cannot be done expeditiously, antibiotic therapy should be started, and the LP performed subsequently**

- Randall G. Fisher, Thomas G. Boyce, Hugh L. Moffe. 5th edition

Diagnosis

- **Unfortunately, even a normal CT scan is not entirely predictive of a safe LP**
- **Other rare complications of LP include spinal subdural hematomas and intracranial hematomas.**
- **The practice of routinely obtaining a head CT scan prior to lumbar puncture has no support in the literature and causes unnecessary delay in institution of treatment as well as unnecessary expense**
- Randall G. Fisher, Thomas G. Boyce, Hugh L. Moffe. δ^{th} edition

LP contraindication

Signs suggesting raised intracranial pressure	Reduced or fluctuating level of consciousness (Glasgow Coma Scale score <9 or a drop of ≥3 points) Relative bradycardia and hypertension Focal neurologic signs Abnormal posture or posturing Unequal, dilated, or poorly responsive pupils Papilledema Abnormal doll's eye reflex
Shock	Defer until stabilization
Extensive or spreading purpura	Defer until shock and coagulopathy
After convulsions	Defer until airway and breathing are stabilized
Coagulation abnormalities	Defer if results of coagulation studies are outside the normal range, platelet count is <100,000/mm^3, or patient is receiving anticoagulant therapy
Local superficial infection at the lumbar puncture site	Defer
Respiratory insufficiency, severe respiratory distress (nonintubated)	Lumbar puncture is contraindicated because of high risk for precipitating respiratory failure

Diagnosis

- **Normally, CSF in children older than ۶ months :**

<۶ WBCs/mm۳ (no polymorphonuclear leukocytes), glucose >۴۵ mg/dL, and protein <۴۵ mg/dL

- **Values for infants <۹۰ days of age with febrile illness but without meningitis: In months ۱, ۲, and ۳ of life,respectively, mean CSF WBCs were ۶, ۳, and ۳ cells/mm۳ and protein ۷۵, ۵۹ and ۴۰ mg/d**

- Sarah S. Long, Larry K. Pickering, Charles G. Prober ·۲۰۱۲ · Medical

Diagnosis

- **Blood contamination of the CSF tends to decrease from the first tube to the last and often produces a difference that can be seen by the naked eye**
- **Additionally, centrifugation of the fluid usually produces a clear supernatant in traumatic tap, whereas xanthochromia persists in cases of subarachnoid hemorrhage.**

- Randall G. Fisher, Thomas G. Boyce, Hugh L. Moffe. 5th edition

Diagnosis

- **Traumatic LP:**
- **Effects of traumatic lumbar puncture of CSF values also have been studied, showing presence of approximately ۲ WBCs/mm۳ and ۱/۱ mg/dL protein for every ۱۰۰۰ RBCs**
- **True CSF WBC: reported CSF WBC-(peripheral WBC*CSF RBC)/peripheral RBC**
- **True CSF Pr: reported CSF pr-(csf RBC*۱/۱)/۱۰۰۰**
- Randall G. Fisher, Thomas G. Boyce, Hugh L. Moffe. ۵th edition

Diagnosis

- **Smear**
- **Bacteria are most likely to be observed in purulent fluid and are rarely seen in CSF with low leukocyte counts.**
- **The exceptions : cases of neonatal meningitis and in immunocompromised patients**
- **Early infection with meningococci or pneumococci occasionally produces a positive Gram stain of the CSF, confirmed by culture, before any remarkable CSF pleocytosis occurs.**

- Randall G. Fisher, Thomas G. Boyce, Hugh L. Moffe. 5th edition

Diagnosis

- **A Gram stain should be done on all spinal fluid specimens with an increased number of WBC.**
- **The percentage of positive smears is ٢٥% with less than ١٠٣CFU/mL, ٦٠% in the range of ١٠٣ to ١٠٥ CFU/mL, and ٩٧% with greater than ١٠٥ CFU/mL**
- Randall G. Fisher, Thomas G. Boyce, Hugh L. Moffe. ٥th edition

SYNDROME	SPINAL FLUID FINDINGS			CONSCIOUSNESS
	LEUKOCYTES (PER mcL)	PROTEIN (mg/dL)	GLUCOSE (mg/dL)	
Purulent meningitis	>1000 (mostly neutrophils)	>100 (high)	<40 (low)	Lethargic to comatose
Nonpurulent meningitis				
Normal glucose subgroup	10 to 500 (Usually lymphocytes)	Normal	>40	Irritable; variable
Low glucose subgroup		Usually high	<40	Lethargic to comatose

Diagnosis

- In meningitis due to mumps virus, the CSF WBC count sometimes exceeds ١٠٠٠ per mcL but is typically mostly lymphocytes
- In enterovirus meningitis, the protein may be slightly elevated or the glucose slightly depressed or the cell count may be >٥٠٠ per mcL with a slight predominance of neutrophils

- Randall G. Fisher, Thomas G. Boyce, Hugh L. Moffe. ٥th edition

Diagnosis

- **CSF Multiplex PCR Tests**
- **Multiplex CSF PCR tests, which can detect several pathogens, often including *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Escherichia coli*, *Klebsiella pneumoniae*, enterovirus, HSV-١ and -٢, EBV, CMV, HHV-٦, and *Cryptococcus*.**
- **These assays are much more useful than latex agglutination testing in the setting of a patient who is pretreated with antibiotics or in resource-poor settings**

Diagnosis & Prior Antibiotic Therapy

- **Antibiotic therapy should not be delayed until the spinal fluid studies are available**
- **Even when children received appropriate antibiotics for meningitis intravenously for ۴۴ to ۶۸ hours, the bacterial character of the chemical and cellular findings could be discerned in most cases.**

Diagnosis & Prior Antibiotic Therapy

- **Complete sterilization of N. meningitidis occurred within ٢ hours of giving a parenteral third-generation cephalosporin and the beginning of sterilization of S. pneumoniae from CSF by ٤ hours into treatment.**

Diagnosis

- **The BMS and out patients management; for children who had pleocytosis (٧ cells/μL or more) and none of the following five criteria on presentation**
- **History of a seizure with the illness, blood neutrophil count of at least ١٠ × ١٠ ٣ cells/μL, positive CSF Gram stain, CSF protein of at least ٨٠ mg/dL, or CSF neutrophil count of at least ١ × ١٠ ٣ cells/μL.**
- **٩٥% sensitivity but failed to identify five patients with bacterial meningitis.**
- https://doi.org/١٠/٢١٤٧٪٢FIDR.S٢٤٠١٦٢

Diagnosis

- **Meningitest, was refined with incorporation of a serum PCT>= ۰/۵ ng/mL or greater and was claimed to have the sensitivity of ۱۰۰% and specificity of ۳۷%**
- https://doi.org/۱۰/۱۰۱۶/j.jpeds.۲۰۰۷/۰۷/۰۱۲
- https://doi.org/۱۰/۱۰۹۷/wco.۰b۰۱۳e۳۲۸۳۲b۲۴۰e

Diagnosis

- **Meningitis score for emergencies (MSE) :**
- **Assigning ٣ points for PCT >١٫٢ ng/dL, ٢ points for CSF protein >٨٠ mg/dL, ١ point for CSF ANC >١٠٠٠ cells per mm٣, and ١ point for (CRP) >٤٠ mg/L**
- **They found an MSE of ≥١ predicted bacterial meningitis**
- **Sensitivity of ١٠٠% , a specificity of ٨٣٫٢% , and a NPP ١٠٠%**

https://doi.org/١٠٫١٥٤٢/peds.٢٠٢٠-١١٢٦

Treatment

PICU:

Hemodynamic instability (ie, septic shock)

Significant respiratory compromise

Prolonged or recurrent seizures

Severely depressed mental status

Rapidly deteriorating clinical status, or other potentially life-threatening complications

Treatment

- **Fluid management**
- **Normovolemia without SIADH :**

Can receive isotonic fluids at a maintenance rate

SIADH:serum sodium < ١٣٠ mEql/l :٢/٣ to ٣/٤of maintenance.

Daily weight, urine output, serum electrolytes, and, if indicated, serum and urine osmolalities should be carefully monitored

Treatment

- **Initial empiric therapy using cefotaxime or ceftriaxone plus vancomycin (٦٠ mg/kg/day divided q٦h) is prudent for infants ≥١ month and children with suspected bacterial meningitis.**
- **Once an organism has been identified and the antimicrobial susceptibility pattern is known, antibiotic therapy can be simplified or modified**

Treatment

- Dexamethasone:
- Hib meningitis: recommended
- For suspected pneumococcus or meningococcus: controversial
- Some experts: (>= ٦ weeks to <= ٥ year) SCD,or hyposplenism

Treatment

- Although many patients with isolates having third-generation cephalosporin MIC of ٠/٥ to ١/٠ μg/mL have been treated successfully, treatment with cephalosporin alone is usually not recommended.
- It is prudent to repeat the CSF examination after ٢٤ to ٤٨ hours of therapy in patients with infection caused by β-lactam-resistant pneumococci to document a sterile culture and negative Gram stain.

Treatment

- **If results of the second CSF Gram stain or culture are positive, or a pneumococcal isolate has an MIC of ≥١/٠ µg/mL for extended-spectrum cephalosporins, vancomycin (if not begun previously) with or without rifampin should be added.**
- **Rifampin should be added if the patient is already receiving vancomycin**

Treatment

- Cefepime and meropenem, both of which have been shown to be equivalent to third-generation cephalosporins in treatment of children infected with common meningeal pathogens
- The efficacy of these antibiotics against β-lactam-resistant pneumococci has not been defined, although they appear not to be superior to cefotaxime or ceftriaxone

Treatment

- At least ٧ days for meningococcus, ١٠ days for pneumococcus, and ١٤ days for *H. influenzae*.
- Patients should generally be afebrile for ٤٨ hours before therapy is stopped.
- For meningitis due to gram-negative organisms (other than *H. influenzae*), the duration is ٢١ days.

Treatment

Patients who receive intravenous or oral antibiotics prior to LP and do not have an identifiable pathogen, but do have evidence of bacterial meningitis based on their CSF profile, should receive therapy with ceftriaxone or cefotaxime for٧-١٠ days

Treatment

- Fever lasts >٥ days in approximately ١٠ to ١٥ percent of patients
- Secondary fever (eg, recurrence of fever after being afebrile for at least ٢٤ hours) occurs in approximately ١٥ to ٢٠ percent

Treatment

- **Inadequate treatment**
- **Development of nosocomial infection (eg, infected [IV] catheters, UTI, viral infection)**
- **Nosocomial infection is more often associated with secondary fever than with persistent fever**
- **Discontinuation of dexamethasone**
- **Development of a suppurative complication (pericarditis, pneumonia, arthritis, subdural empyema**
- **Drug fever**

Fallow up

- Hearing evaluation
- Hearing evaluation should be performed at the time of or shortly after discharge from the hospital discharge
- Developmental Screening
- Young children who have been treated for meningitis are at risk for developmental delay. Developmental surveillance should continue throughout childhood

Prevention

- **Close contacts of patients with meningococcal disease should receive chemoprophylaxis with rifampin (٥ mg/kg if <١ month of age, ١٠ mg/kg if ≥١ month of age; maximum dose ٦٠٠ mg) twice daily for ٢ days, started ideally within ٢٤ hours of the exposure.**
- **A single large oral dose of ciprofloxacin (٢٠ mg/kg, maximum ٥٠٠ mg) or azithromycin (١٠ mg/kg, maximum ٥٠٠ mg) or a parenteral dose of ceftriaxone (١٢٥ mg IM if <١٥ years, ٢٥٠ mg IM if ≥١٥ years) are suitable alternatives; the last is preferred for pregnant women.**

Prevention

- **Close contact:**
- **Generally refers to individuals who have had prolonged (>٨ hours) contact while in close proximity (<٣ feet) to the patient or who have been directly exposed to the patient's oral secretions during the seven days before the onset of the patient's symptoms and until ٢٤ hours after initiation of appropriate antibiotic therapy**

Prevention

- Household members, roommates, intimate contacts, contacts at a childcare center, young adults exposed in dormitories, military recruits exposed in training centers
- Travelers who had direct contact with respiratory secretions from an index patient or who were seated directly next to an index patient on a prolonged flight (ie, one lasting ≥^ hours)

Prevention

- Individuals who have been exposed to oral secretions (eg, intimate kissing, mouth-to-mouth resuscitation, endotracheal intubation, or endotracheal tube management)

Prevention

- **Rifampin prophylaxis also is recommended for all household contacts of an index case with Hib disease when at least one household contact is younger than ۴ years and is unimmunized or incompletely immunized**

Prevention

- **Vaccination: Hib, S. pneumonia**
- **Children at high risk for meningococcal infection, such as those with asplenia or persistent complement deficiencies, should receive MCV۴ at ۲ years of age and every ۵ years thereafter.**
- **All adolescents should receive MCV۴ at ۱۱ to ۱۲ years of age, with a booster at ۱۶ years of age**

Thanks for your Consideration