Meningitis

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Objectives

- Pathogenesis & pathophysiology
- Epidemiology
- Microbiology
- Clinical presentation
- Laboratory work up
- Management
- Complications
- Outcomes

Pathogenesis & Pathophysiology

- Complex interplay between virulence factors of the pathogens and the host immune response
- Much of the damage is from cytokines released within the CSF and the host inflammatory response

Pathogenesis & Pathophysiology

Predisposing Factors

- The CSF has 1000-fold lower levels of immunoglobulins and complement than serum
  - Poor opsonic activity
  - Successful bacterial replication
  - The subsequent development of inflammation
- Strep pneumonia has a virulence capsule which facilitates colonization and prevents opsonization
- Subcapsular bacterial surface components induce CSF inflammation and blood-brain barrier injury.

Pathogenesis & Pathophysiology

Predisposing Factors

- Inflammatory components induced within the CSF:

Interleukin-1 [IL-1], IL-6, and tumor necrosis factor-alpha) and matrix metalloproteinases

- Inflammation injures the endothelium of the blood-brain barrier (eg, separation of intercellular tight junctions) leading to vasogenic brain edema, loss of cerebrovascular autoregulation, and increased intracranial pressure.
- This results in localized areas of brain ischemia, cytotoxic injury, and neuronal apoptosis.

How it is acquired

Blood Borne

- Colonization of respiratory, gastrointestinal, or lower genital tract by bacteria which have fimbriae or pili to help them adhere to the mucus membranes)
  - Invasion of the bloodstream
  - Survival in the bloodstream (*S. pneumoniae, N. meningitidis, H. influenzae*, GBS, and *E. coli all have a* polysaccharide capsule to protect them)
  - Entry into the subarachnoid space where IG and complement is 1000-fold lower than serum)

Pathogenesis & Pathophysiology

Or Direct entry

- Contiguous infection (sinusitis, mastoiditis, periorbital cellulitis)
- Trauma, neurosurgery, or cerebrospinal fluid (CSF) leak
- Medical devices (CSF shunts, cochlear implants)

Increased Susceptibility and RiskFactors

- Congenital or acquired immunodeficiency
  - asplenia
  - complement deficiency
  - hypogammaglobulinemia
  - HIV infection
  - glucocorticoid use
  - diabetes mellitus
- Anatomic defects of the brain, spinal cord or inner ear(dermal sinus)
- Recent infection (especially respiratory and ear infections)
- Recent exposure to someone with meningitis (chemoprophylaxis)
- Recent travel to an area with endemic meningococcal disease, such as sub-Saharan Africa

Incidence

(USA 2006)

- *<2 months – 81 per 100,000 population*
- 2 months to 2 years – 7 per 100,000 population
- 2 through 10 years – 0.6 per 100,000 population
- 11 through 17 years – 0.4 per 100,000 population

Microbiology Neonates

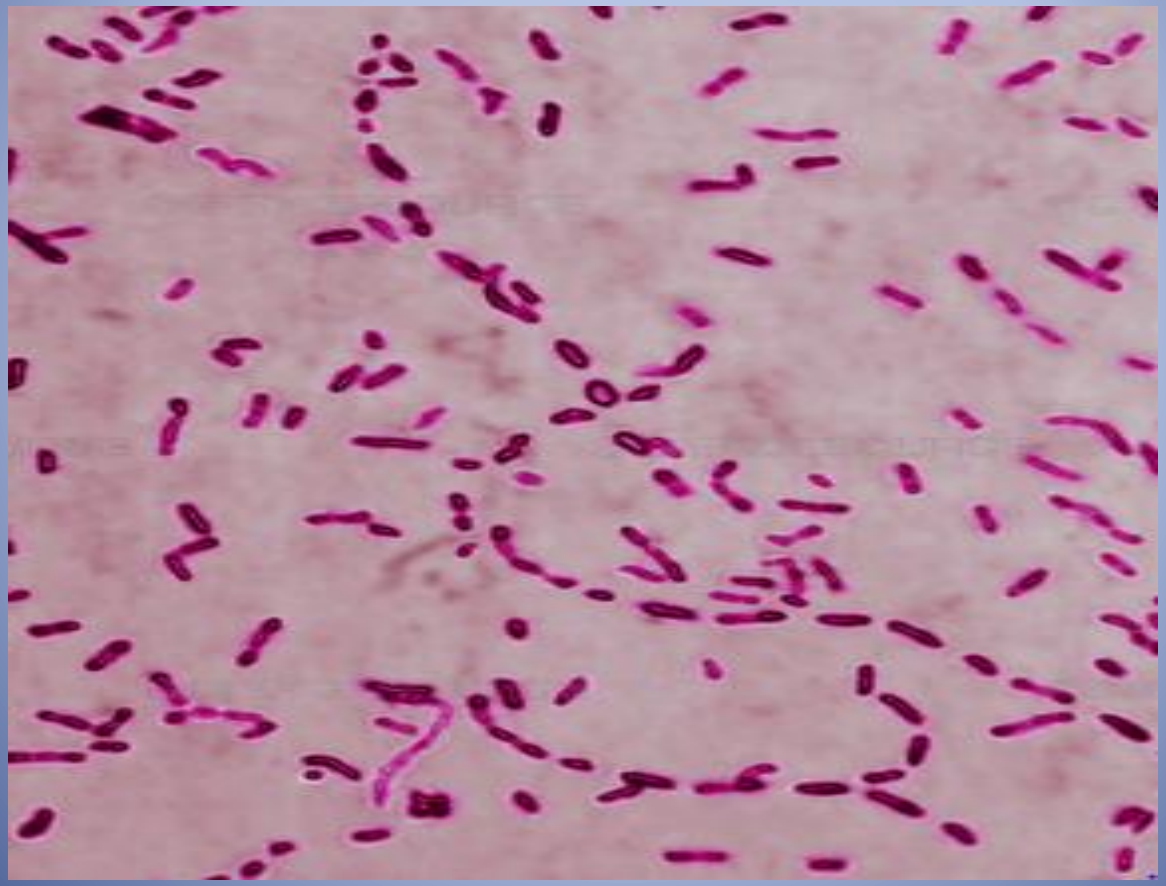
- **Infants <3 months**
  - Group B streptococcus (GBS)
  - *Escherichia coli*
- GBS and *E. coli* account for approximately 65 to 75 percent of all cases of early-onset meningitis (ie, onset within 72 hours of birth)
- When *E. coli* meningitis occurs *after six days of age, galactosemia* should be excluded.

  - CoNS, *Enterococcus*, *Listeria*, *N. meningitides*, nontypeable *H. influenzae*, *S. aureus*, *S. pneumoniae*, other streptococci (groups A, C, or G and viridans streptococci)

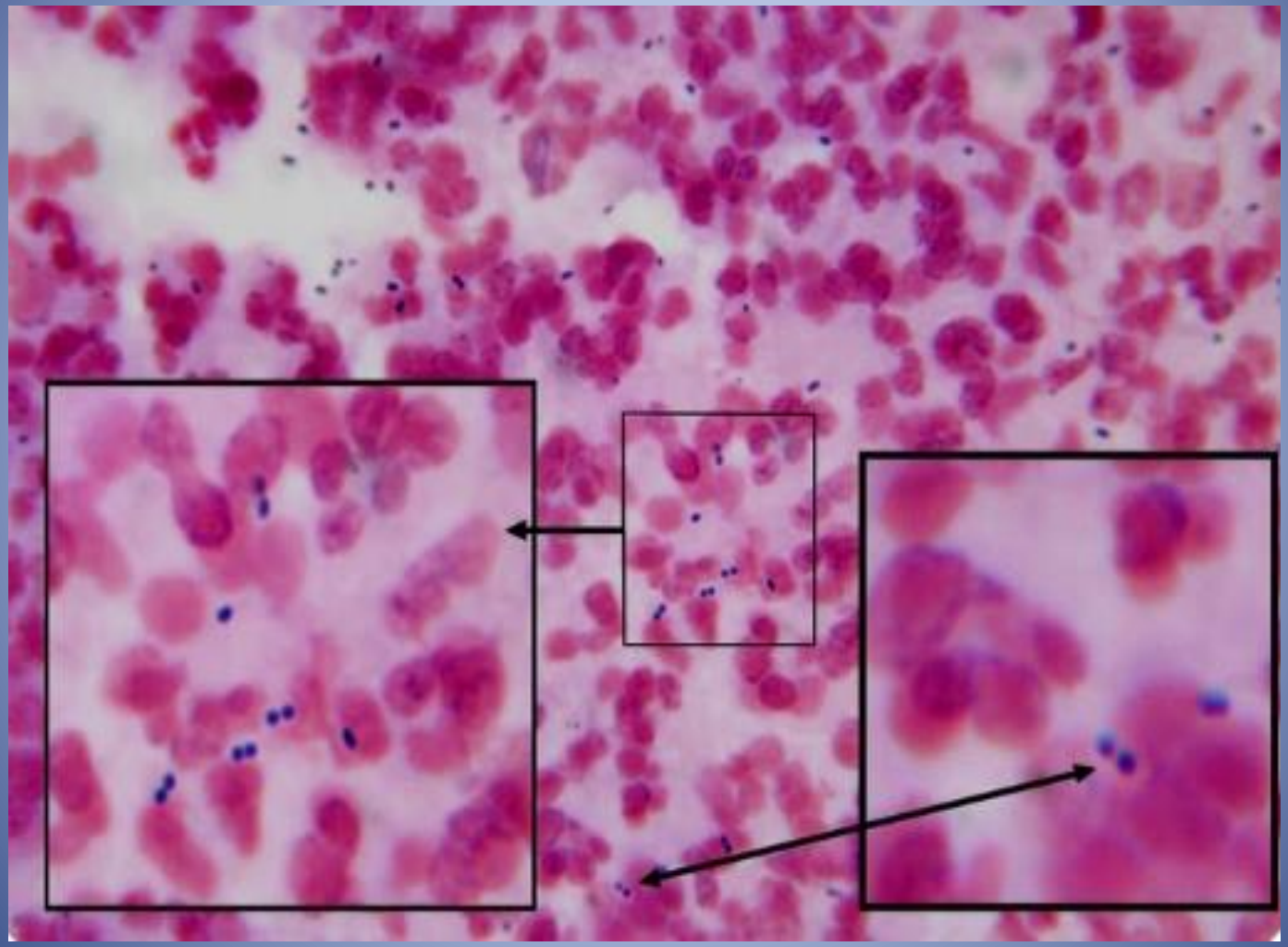
Microbiology

- **Older infants and children**
  - *S. pneumoniae*
  - *N. meningitidis*
  - *H. influenzae*, and other gram-negative organisms.
- **Adolescents**
  - *N. meningitidis*

Haemophilus Influenzae B



Streptoccocus Pneumoniae



Microbiology

Characteristic features of common causes of bacterial meningitis

Organism	Site of entry	Age range	Predisposing conditions
Neisseria meningitidis	Nasopharynx	All ages	Usually none, rarely complement deficiency
Streptococcus pneumoniae	Nasopharynx, direct extension across skull fracture, or from contiguous or distant foci of infection	All ages	All conditions that predispose to pneumococcal bacteremia, fracture of cribriform plate, cochlear implants, cerebrospinal fluid otorrhea from basilar skull fracture, defects of the ear ossicle (Mondini defect)
Listeria monocytogenes	Gastrointestinal tract, placenta	Older adults and neonates	Defects in cell-mediated immunity (eg, glucocorticoids, transplantation [especially renal transplantation]), pregnancy, liver disease, alcoholism, malignancy
Coagulase-negative staphylococci	Foreign body	All ages	Surgery and foreign body, especially ventricular drains; dermal sinus
Staphylococcus aureus	Bacteremia, foreign body, skin	All ages	Endocarditis; surgery and foreign body, especially ventricular drains; cellulitis; dermal sinus; decubitus ulcer
Gram-negative bacilli	Various	Older adults and neonates	Advanced medical illness, neurosurgery, ventricular drains, disseminated strongyloidiasis
Haemophilus influenzae	Nasopharynx, contiguous spread from local infection	Adults; infants and children if not vaccinated	Diminished humoral immunity

Graphic 73706 Version 9.0

Clinical presentation
Neonates

- Poor feeding or vomiting – 50 percent
- Decreased activity – 50 percent
- Respiratory distress (tachypnea, grunting, flaring of the nasal alae, retractions, decreased breath sounds) – 33 to 50 percent
- Apnea – 10 to 30 percent
- Change in stool frequency or consistency – 20 percent

Clinical presentation Neonates

- Temperature instability
- CNS findings:
  - Irritability (60%) , lethargy, poor tone, twitching, tremor
  - Seizures in 20-50% usually *focal and atypical* (lip smacking or eye deviation)
  - Bulging fontanelle 25% and
  - Nuchal rigidity 15% are **not** common findings

Evaluation Neonates

- Review of the prenatal and birth history
- •Complete physical examination
- •Full laboratory evaluation for *sepsis* including:
  - -Complete blood count with differential
  - KFT/LFT
  - -Blood culture
  - -Urine culture (if ≥72 hours old)
  - -Lumbar puncture (LP) for cerebrospinal fluid (CSF) cell count, protein, glucose, Gram stain, culture, and molecular testing

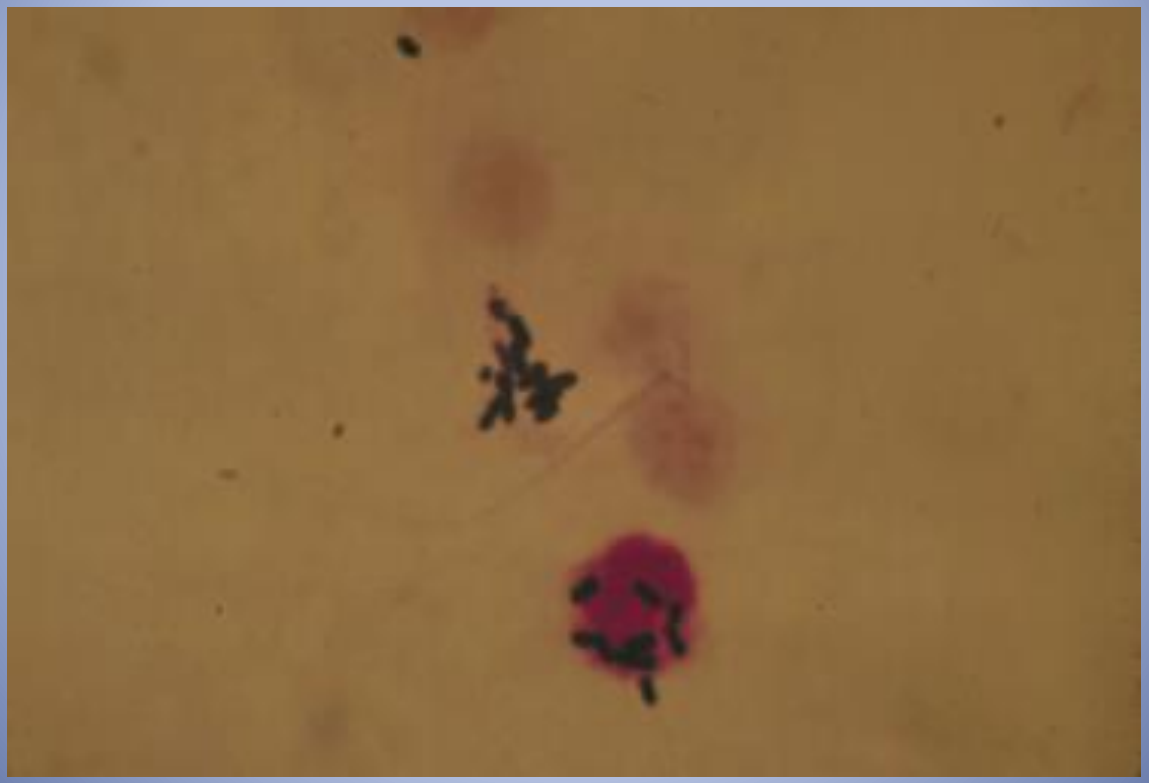
Evaluation CSF Neonates

- CSF white blood cell (WBC) count >15-20 cells/microL with a neutrophilic predominance
- Elevated CSF protein(CSF protein levels >100 mg/dL in term neonates and >125 to 150 mg/dL in preterm neonates are consistent with bacterial meningitis)
- Decreased CSF glucose <60 percent of the blood glucose level or <30 mg/dL [1.7 mmol/L] in a term infant or <20 mg/dL [1.1 mmol/L] in a preterm infant) is consistent with bacterial meningitis

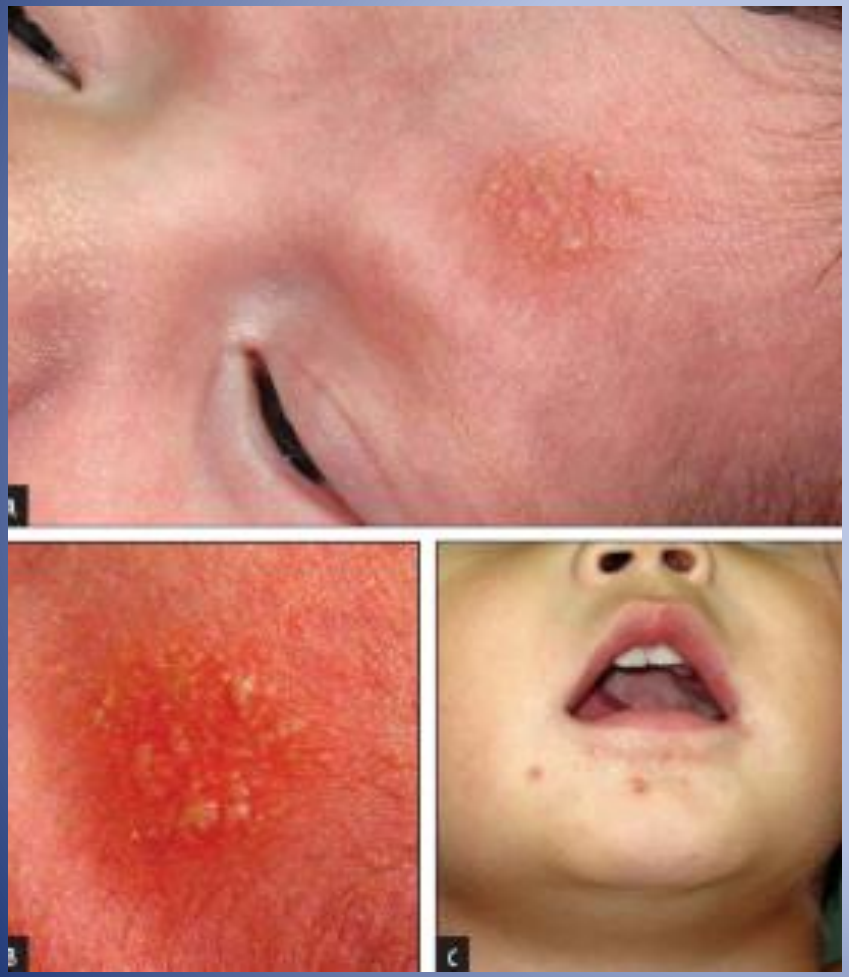
Evaluation CSF Neonates

- Gram stain
- Molecular tests : e.g. FilmArray ME panel tests for 14 different pathogens, including group B *Streptococcus*, *E. coli* (K1 serotype only), *Listeria monocytogenes*, *Haemophilus influenzae*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, HSV-1, HSV-2, CMV, enterovirus, human parechovirus, human herpesvirus 6, varicella zoster virus, and *Cryptococcus*.
- CSF HSV PCR plus additional blood tests and surface viral cultures.

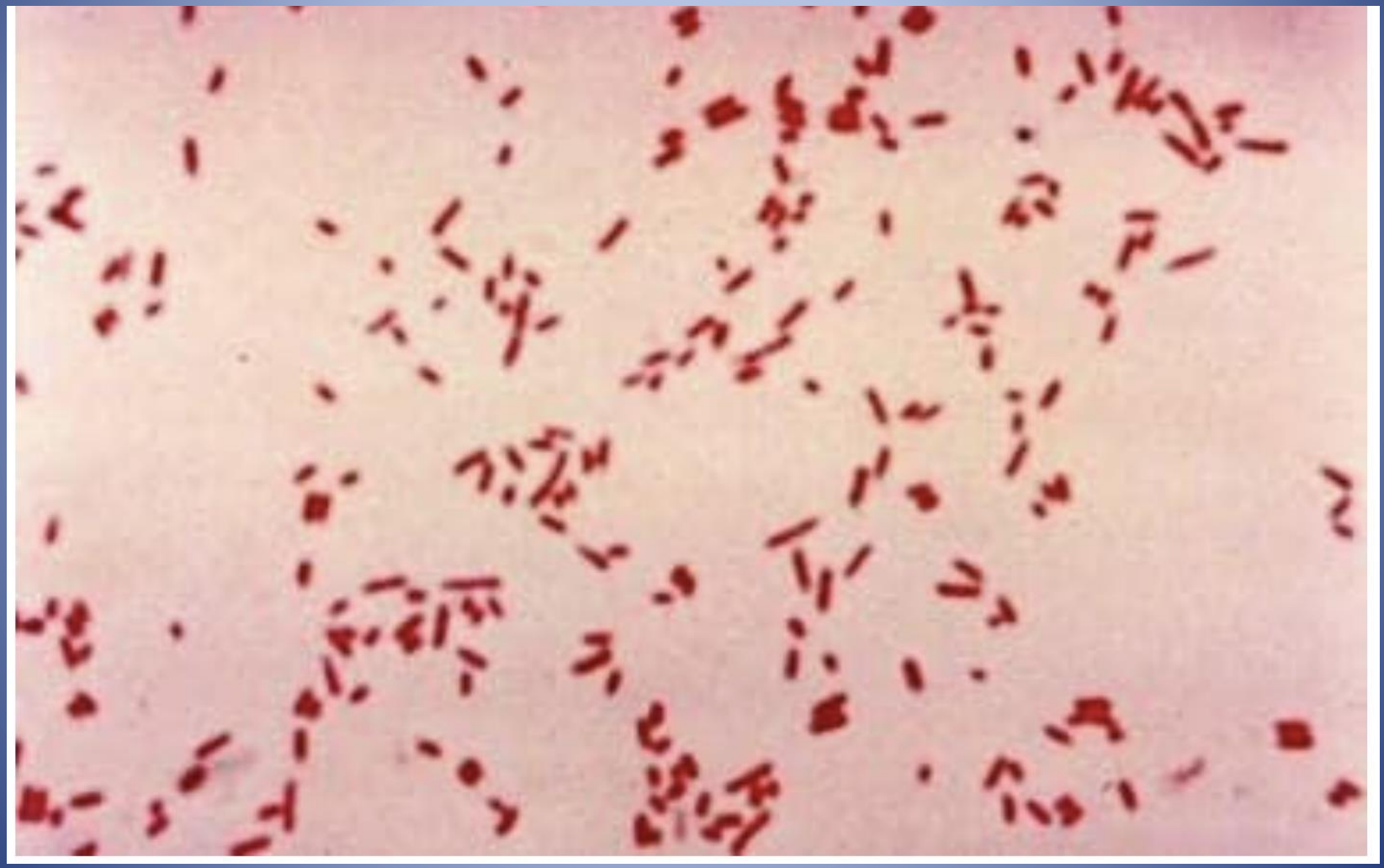
GBS



HSV



E. Coli



Clinical presentation
Infants

Infants :

- Fever or hypothermia
- Poor feeding
- Irritability
- Vomiting
- Diarrhea
- Respiratory distress
- Jaundice
- Lethargy
- Bulging Fontanelle
- Seizures

Clinical presentation
Children and adolescents

- Fever
- • Meningeal irritation signs
- •Nausea/vomiting
- •Confusion
- •Lethargy
- •Irritability

Meningeal Irritation signs

- Nuchal rigidity
- Headache,
- Photophobia
- Irritability

- Nuchal rigidity
  - Inability to place the chin on the chest
  - Limitation of passive neck flexion
  - Kernig sign – Kernig sign is present if the patient, in the supine position with the hip and knee flexed at 90°, cannot extend the knee more than 135° and/or there is flexion of the opposite knee
  - •Brudzinski sign – Brudzinski sign is present if the patient, while in the supine position, flexes the lower extremities during attempted passive flexion of the neck

Neurologic signs

- Abnormal Mental Status
- Seizures in 20-30%
- Increased ICP:
  - Bulging fontanelle
  - Diastasis if sutures
  - Paralysis of 3rd,4th, or 6th cranial nerves
  - Papilledema

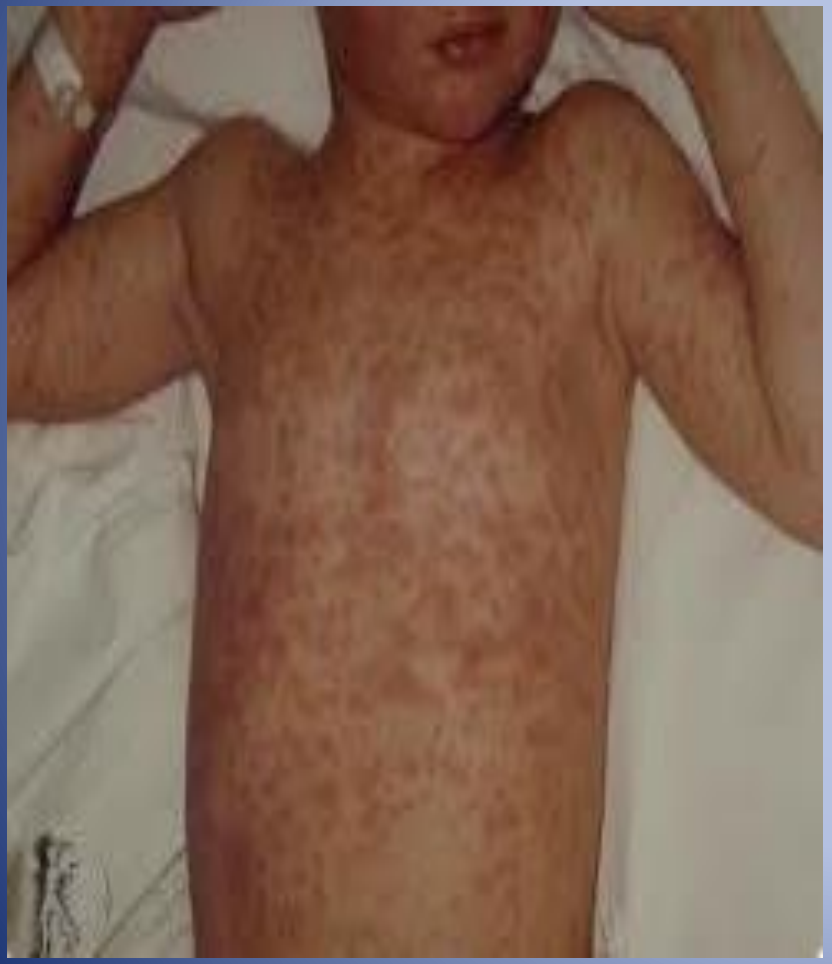
Focal neurologic findings

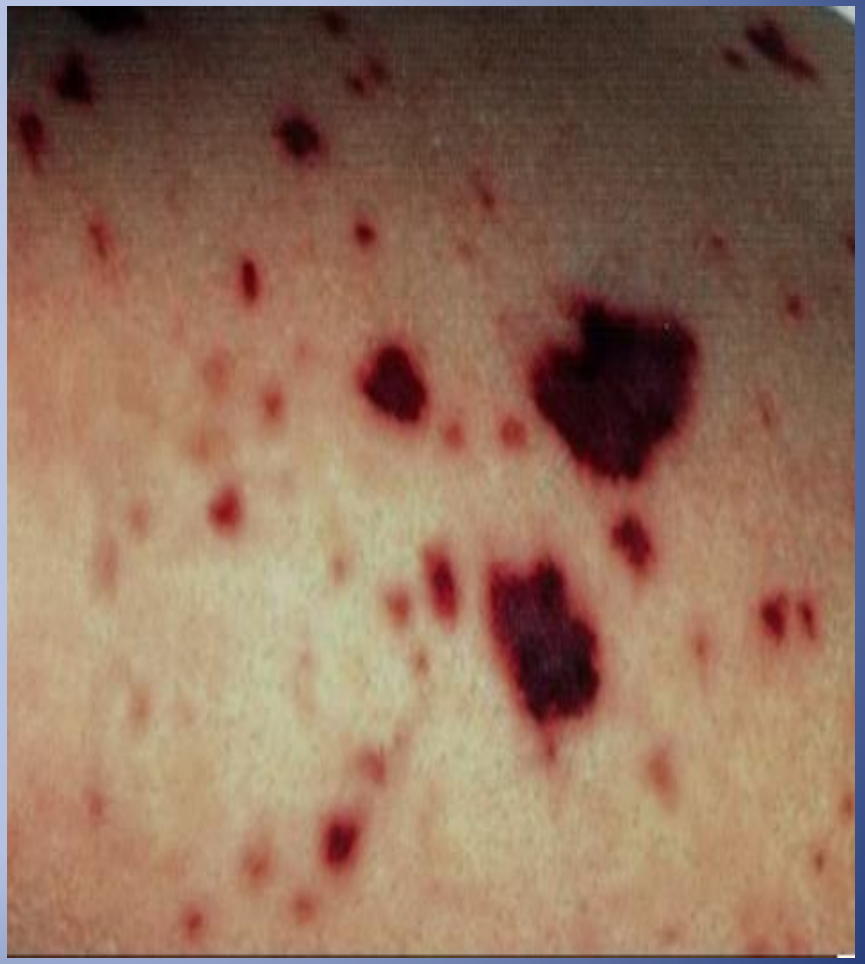
- Hemiparesis, quadriparesis
- Asymmetric or absent tendon reflexes
- Cranial nerve palsies (eg, abnormal pupillary light response, visual field defects, eye deviation or abnormal extraocular movements, facial asymmetry).

Other signs depending on causative organism

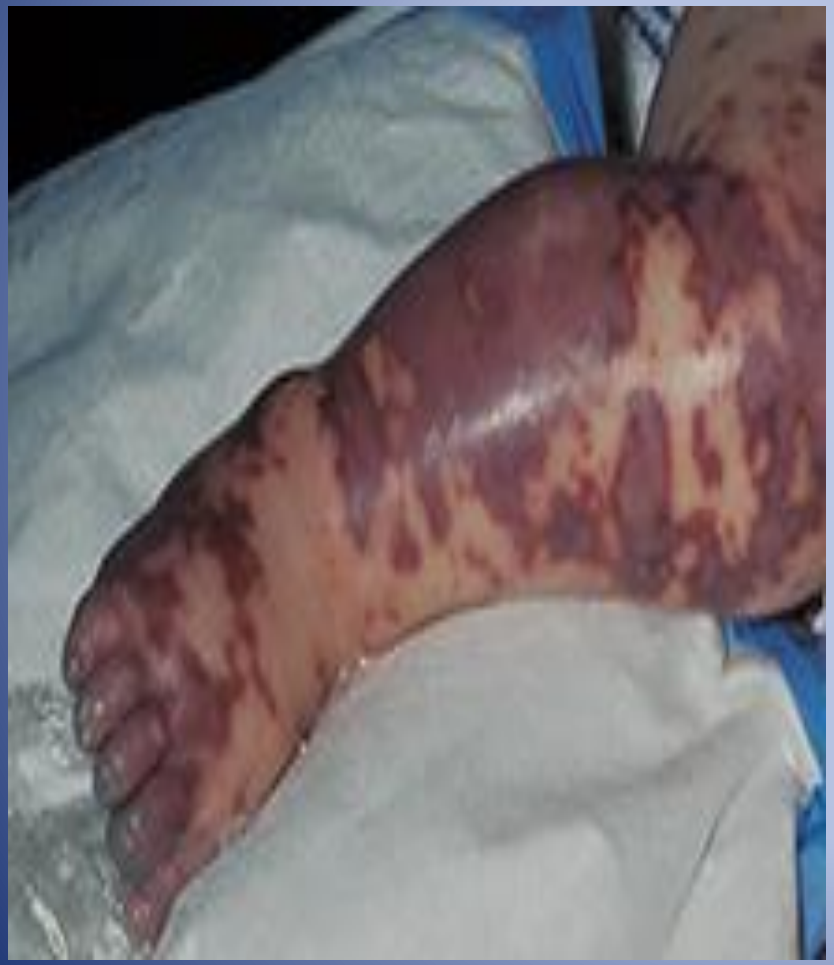
- Skin rashes
- Focal Infections: OM, mastoiditis, pneumonia
- Fever and chills
- Septic shock
- DIC disseminated intravascular coagulation
- Acute respiratory distress syndrome
- Pericardial effusion
- Septic or reactive arthritis

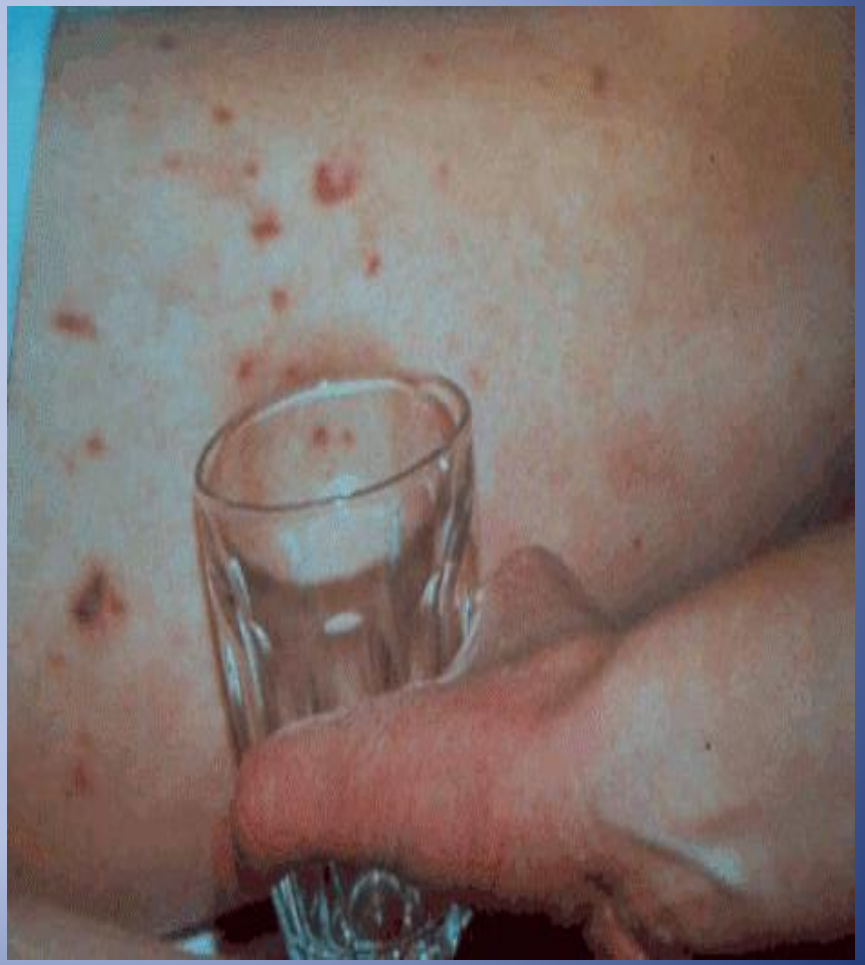
Meningococcal Rash



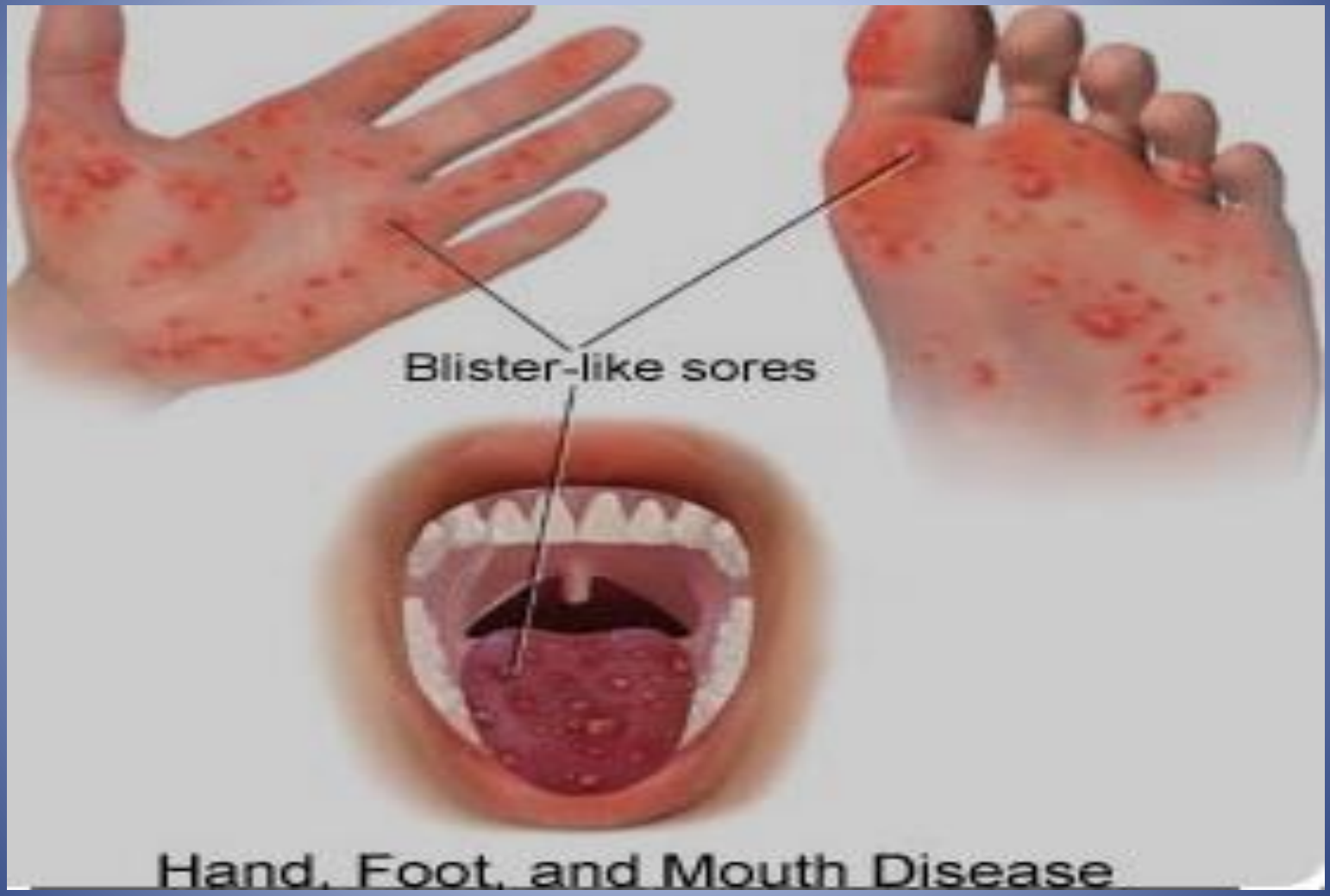


Meningococcal Rash

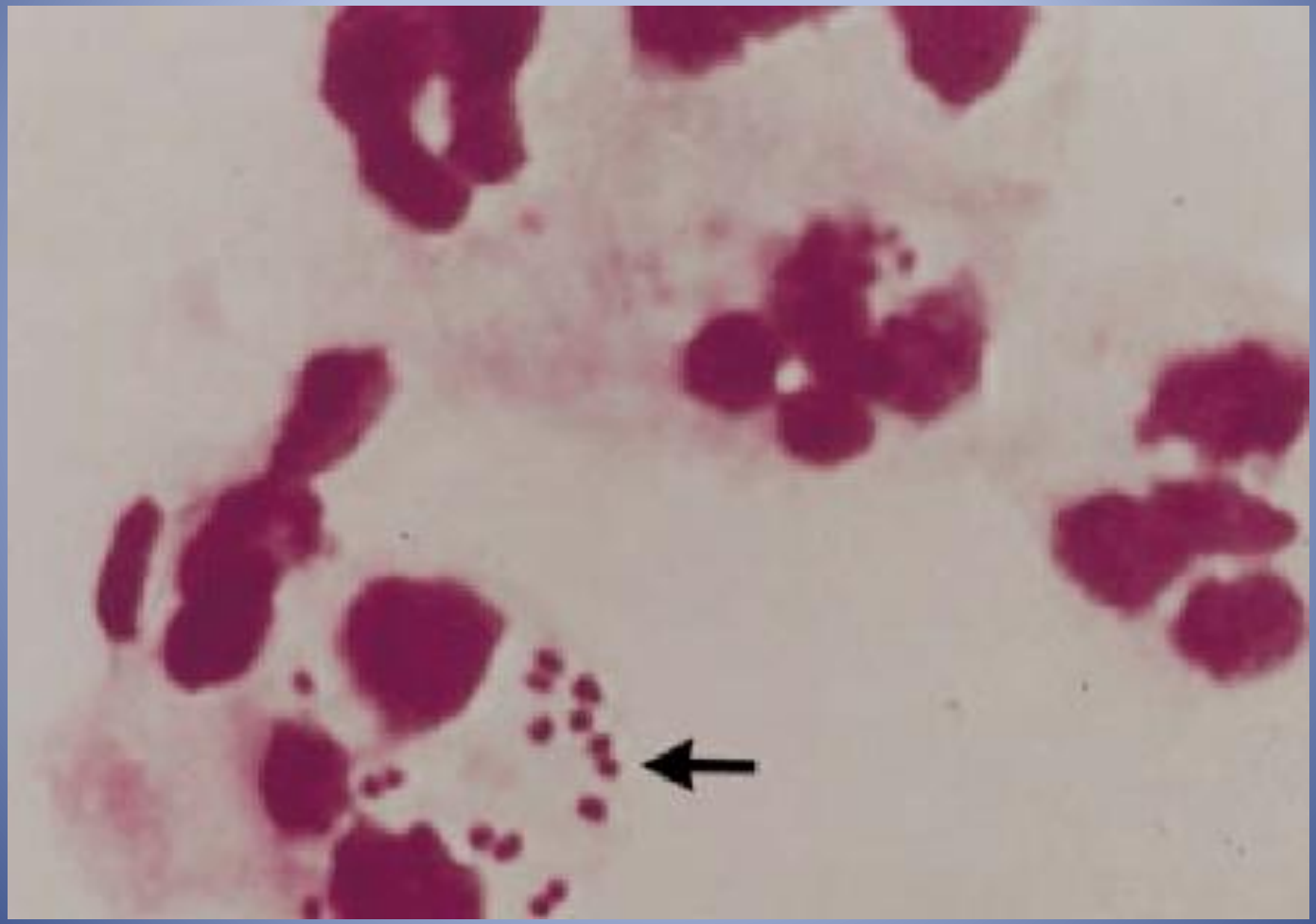




Enteroviruses



Nisseria Meningitidis



Laboratory testing
General

- Blood culture.
- CBC with differential and platelet count.
- Inflammatory markers (CRP, procalcitonin).
- Serum electrolytes, BUN, creatinine, glucose.
- PT, INR, and PTT

Laboratory testing
Neonate

Lumbar puncture

- Cell count and differential)
- Protein and glucose
- Gram stain and culture
- Multiplex PCR testing
- Herpes simplex virus (HSV) PCR if there are clinical concerns for HSV infection and/or CSF pleocytosis

Contraindications to LP

- Baby is clinically unstable

Laboratory testing older babies and children

Lumbar puncture

- cell count and differential
- glucose
- protein concentration
- Gram stain
- Culture
- PCR (Strep pneumoniae ,MRSA , HSV, Enteroviruses)

Contraindications to LP

- cardiopulmonary compromise,
- clinical signs of increased intracranial pressure,
- papilledema,
- focal neurologic signs, and
- skin infection over the site for LP.

CSF in Bacterial Meningitis

- Opening pressure 200-500 mm H2O
- White blood cell count 1000-5000/mm3
  Percentage of neutrophils >80%
- Protein 100-500 mg/dL
- Glucose <40 mg/dL
- CSF : serum glucose <0.4

Typical cerebrospinal fluid findings in central nervous system infections*

	Glucose (mg/dL)		Protein (mg/dL)		Total white blood cell count (cells/microL)		
	<10¶	10 to 40Δ	100 to 500◇	50 to 300§	>1000	100 to 1000	5 to 100
More common	Bacterial meningitis	Bacterial meningitis	Bacterial meningitis	Viral meningitis Nervous system Lyme disease (neuroborreliosis) Encephalitis Neurosyphilis TB meningitis¥	Bacterial meningitis	Bacterial or viral meningitis TB meningitis	Early bacterial meningitis Viral meningitis Neurosyphilis TB meningitis
Less common	TB meningitis Fungal meningitis	Neurosyphilis Some viral infections (such as mumps and LCMV)		Early bacterial meningitis	Some cases of mumps and LCMV	Encephalitis	Encephalitis

TB: tuberculosis; LCMV: lymphocytic choriomeningitis virus.

* It is important to note that the spectrum of cerebrospinal fluid values in bacterial meningitis is so wide that the absence of one or more of these findings is of little value. Refer to the UpToDate topic reviews on bacterial meningitis for additional details.

¶ <0.6 mmol/L.

Δ 0.6 to 2.2 mmol/L.

◇ 1 to 5 g/L.

Clinical and laboratory features of viral and bacterial meningitis in children

Feature	Viral meningitis	Bacterial meningitis
Seasonal pattern	Enteroviral infections (the most common cause of viral meningitis) occur mostly in summer and fall	No characteristic seasonal pattern
Clinical features		
Fever, headache, stiff neck, photophobia	Common	Common
Ill appearance	Uncommon	Common
Petechiae or purpura	Absent	May be present
Other manifestations of enteroviral infection (eg, rash, conjunctivitis, herpangina, pharyngitis)	Common	Uncommon
Symptoms after LP	Often, there is improvement	No improvement
CSF parameters		
WBC count	Typically 10 to 500 cells/microL	Typically >1000 cells/microL, but can be lower, particularly early in the course
Differential	Mononuclear predominance	Neutrophil predominance
Glucose	Normal or slightly reduced Usually ≥40% of serum value	Usually <60% of serum value Often <40 mg/dL
Protein	Normal to slightly elevated Usually <150 mg/dL	Typically 100 to 500 mg/dL

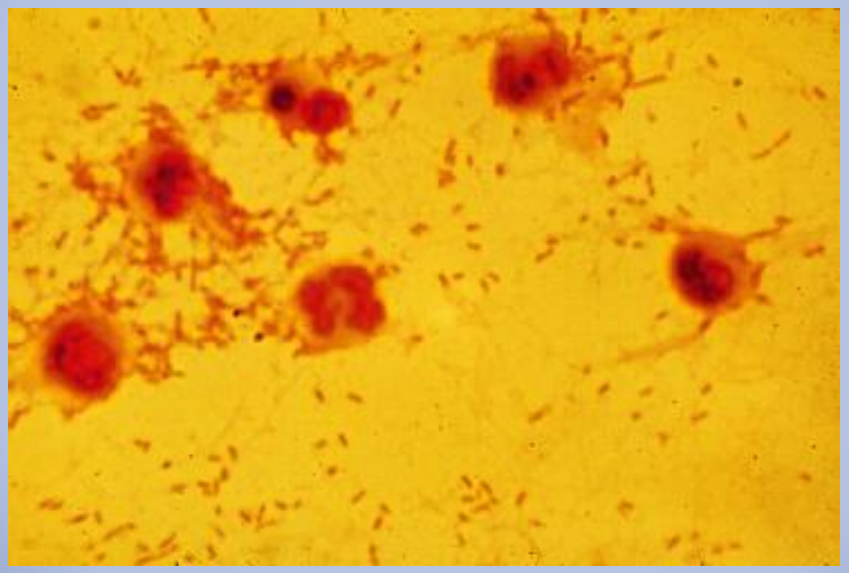
This table summarizes the typical findings in viral and bacterial meningitis in children. However, there is considerable overlap between the two

Gram Stain of CSF

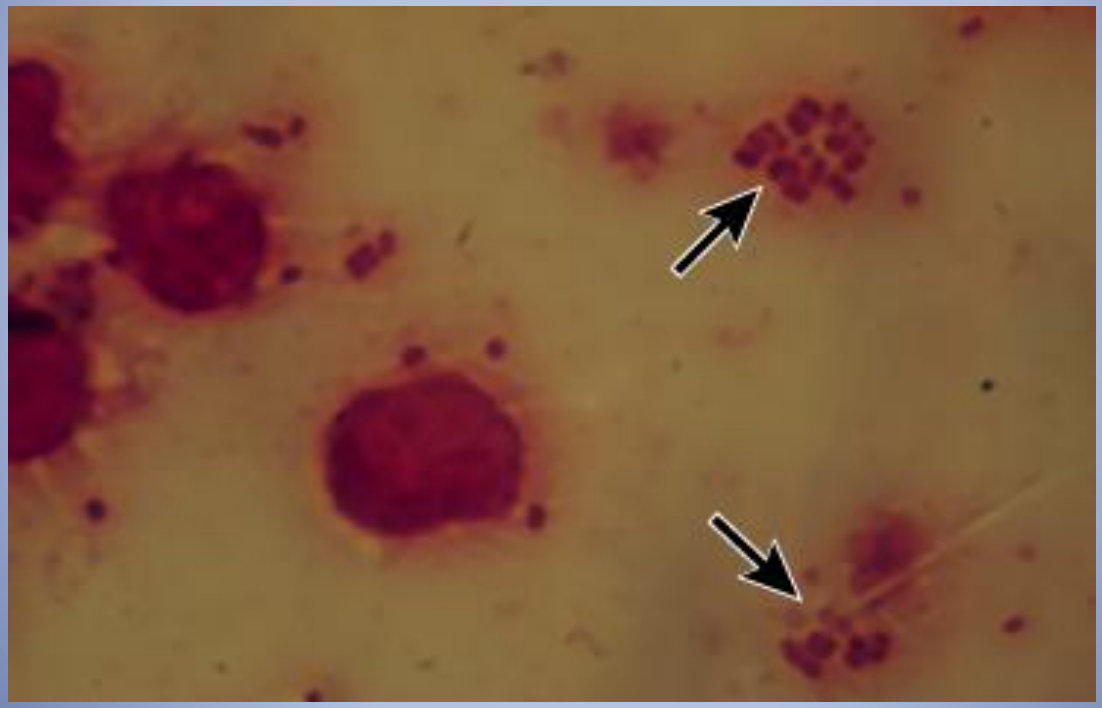
Characteristic morphologic features of the common pathogens

- Gram-positive diplococci suggest *S. pneumoniae*
- Gram-negative diplococci suggest *N. meningitidis*
- Small pleomorphic gram-negative coccobacilli suggest Hib
- Gram-positive cocci or coccobacilli suggest group B streptococcus (GBS)
- Gram-positive rods and coccobacilli suggest *L. monocytogenes*

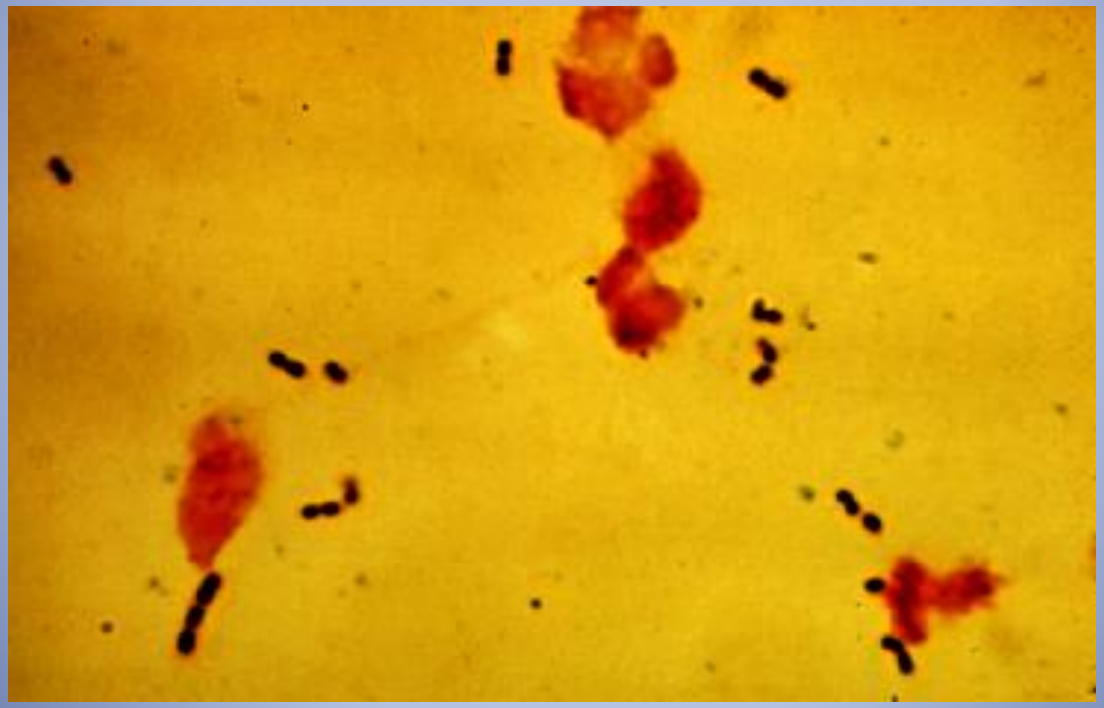
Hib



N. meninigitidis



S. pneumoniae



Neuroimaging

Indications for neuroimaging *before* LP

- severely depressed mental status (coma)
- papilledema
- focal neurologic deficit (with the exception of cranial nerve VI or VII palsy)
- history of hydrocephalus and/or presence of a CSF shunt
- recent history of CNS trauma or neurosurgery

Management

Supportive care

- Ensure adequate oxygenation, ventilation, and circulation
- Obtain venous access
- Cardio-respiratory monitoring while obtaining laboratory studies.
- Keep the head of bed elevated at 15 to 20°.
- Treat hypoglycemia, acidosis, and coagulopathy

Antibiotic Treatment

Antimicrobial therapy

- Antibiotic therapy should be **initiated immediately** following the LP if the clinical suspicion for meningitis is high
- For most patients
- •Vancomycin 60 mg/kg/day IV (maximum dose 4 g/day) in four divided doses, **plus**
- •Ceftriaxone 100 mg/kg/day IV (maximum dose 4 g/day) in two divided doses, **or** cefotaxime (where available) 300 mg/kg/day IV (maximum dose 12 g/day) in three or four divided doses
- Give the ceftriaxone twice daily dosing rather than once daily to avoid the possibility of missing a dose dosing errors, delayed doses, or missed doses.

Antibiotic treatment of of Neonates

Empiric therapy	
Early onset (<72 hours)	Ampicillin **and** an aminoglycoside (typically gentamicin)*
Late onset (≥72 hours) – Admitted from the community	Preferred regimen – Ampicillin **and** an aminoglycoside (typically gentamicin)* Alternative – Ampicillin **and** an expanded-spectrum cephalosporin (eg, ceftazidime, cefepime, or cefotaxime [where available])
Late onset (≥72 hours) – Hospitalized since birth	Vancomycin **or** nafcillin/oxacillin[¶], **and** An aminoglycoside (typically gentamicin)*
Special circumstances:	
Suspected meningitis (eg, CSF pleocytosis)	Same as above except substitute an expanded-spectrum cephalosporin (eg, ceftazidime, cefepime, or cefotaxime [where available]) for the aminoglycoside[Δ]

Antibiotic treatment of of Neonates AAP recommendations 2024

- IV ampicillin with ceftazidime for treatment of meningitis in well-appearing infants age 8 to 28 days
- Ceftriaxone and vancomycin for infants between 29 and 60 days of age

Dexamethasone use

- **Indication for Dexamethasone in Children**
- **Age**: Infants **≥ 6 weeks** and children.
- **Timing**: Give **before or within 10–20 minutes** of the first antibiotic dose.
- **Benefit**: Reduces risk of hearing loss and mortality, especially in **S. pneumoniae** and **H. influenzae type b** meningitis cdc.gov+15aafp.org+15publications.aap.org+15.

Dexamethasone use

- **When *Not* to Use Dexamethasone**
- **Neonates & infants < 6 weeks**: Not indicated—risks (e.g., hippocampal apoptosis) outweigh benefits publications.aap.org+2publications.aap.org+2cdc.gov+2.
- **Non-bacterial (viral/aseptic) meningitis**: Stop dexamethasone once CSF excludes H. influenzae/S. pneumoniae .
- **After antibiotic administration**: Initiating steroids after antibiotics have begun likely offers no benefit emedicine.medscape.com+6uspharmacist.com+6aafp.org+6.

Dexamethasone use

- **Recommended Dosing Regimen**
- **Dose**: 0.15 mg/kg IV every 6 hours (total ~0.6 mg/kg/day).
- **Duration**: Typically **4 days**, discontinue earlier if bacterial etiology ruled out
- **Administration**: Start 10–20 minutes before or with first antibiotic dose

Dexamethasone use

Summary Table

Patient Group	Use Dexamethasone?	Dose & Timing	Continue If…
≥ 6 weeks, suspected bacterial	✅ Yes	0.15 mg/kg IV q6h x 4d, start before/with antibiotics	Hib or pneumococcus confirmed
< 6 weeks (neonate/young infant)	❌ No	–	–
Aseptic/viral meningitis	❌ No → stop early	–	–
Antibiotics already given	❌ No benefit	–	–

Duration of Therapy

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

Duration of Therapy

- **Treatment duration** — The duration of antimicrobial therapy depends upon the causative organism and clinical course.
- ●*S. pneumoniae* – 10 to 14 days
- ●*N. meningitidis* – 5 to 7 days
- ●*H. influenzae* – 7 to 10 days
- S agalactiae (GBS) 14 days

- ●*L. monocytogenes* – 21 to 28 days (Amp and Gent)
- ●*S. aureus* – At least two weeks
- ●Gram-negative bacilli – Three weeks or a minimum of two weeks beyond the first sterile CSF culture, whichever is longer
-

Clinical Course Uncomplicated

- Fevers typically last three to six days after initiating adequate therapy Fever lasts >5 days in approximately 10 to 15 percent of patients

Clinical Course
Secondary fever

- Secondary fever (recurrence of fever after being afebrile for at least 24 hours) occurs in approximately 15 to 20 percent.
- Possible causes include:
  - Inadequate or incorrect treatment
  - Development of a nosocomial infection (eg, infected intravenous catheters, urinary tract infection, viral infection
  - Discontinuation of dexamethasone
  - ●Development of a suppurative complication (pericarditis, pneumonia, arthritis, subdural empyema
  - ●Drug fever (a diagnosis of exclusion)

Complications

- In patients with persistent or secondary fever, suppurative and nosocomial complications should be carefully sought.
- Death 3-5%
- Subdural effusion/empyema
- Hearing deficit 7-30%
- Decreased IQ 30-50%
- Seizures
- Hemiparesis
- Other neurological deficits

Prognosis

- Case-fatality rates according to the organism isolated are as follows
- ●*H. influenzae* type b (Hib) – 4 to 5 percent
- ●*N. meningitidis* – 7 percent
- ●*S. pneumoniae* – 7 to 15 percent

Chemoprophylaxis in Meningococcal Meningitis

- **Chemoprophylaxis is indicated in close contacts of patients with meningococcal infection.**
- Give **as early as possible**, ideally **within 24 hours** of identifying the index patient.
- Limited or no benefit if given **>14 days** after exposure.

- **Close contacts include**:
- Household members, roommates, intimate contacts
- Childcare center / preschool contacts (within 7 days before onset)
- Dormitory residents, military recruits
- Travelers seated directly next to an index case on flights ≥8 hours
- Anyone exposed to **oral secretions** (e.g., kissing, mouth-to-mouth resuscitation, intubation, suctioning)
- Healthcare workers **only if** directly exposed to oral/respiratory secretions

- **Not indicated**:
- Brief exposures without direct contact
- Most healthcare workers unless exposed to secretions
- **Cultures**: Oropharyngeal/nasopharyngeal cultures are **not helpful** and should not delay prophylaxis.
-

Chemoprophylaxis in Meningococcal Meningitis

- **Timing**
- **Urgent**: Start immediately, ideally <24 hours.
- **Secondary cases** usually occur within **10 days** of the primary case.
- During outbreaks, prophylaxis should **not be delayed** even before confirmation if meningococcal disease is strongly suspected.
- **Regimens**
- **Preferred agents** (CDC guidance):
- **Rifampin** (oral, 2 days)
- **Ceftriaxone** (IM, single dose)
- **Ciprofloxacin** (oral, single dose; avoid if local resistance >20% or multiple resistant cases reported)
- **Alternative**:
- **Azithromycin** (oral, single dose) – use if resistance or contraindications to first-line drugs.
-

- **Resistance Considerations**
- Rising **ciprofloxacin resistance** reported in multiple regions.
- Avoid ciprofloxacin in areas meeting CDC thresholds (≥2 resistant cases or ≥20% resistant isolates in past 12 months).
-

HiB meningitis Prophulaxis

-
- **Who is a "close contact"?**
- Lives with index patient **OR** spent ≥4 hrs/day with them for ≥5 of 7 days before admission
-
- **When to give chemoprophylaxis to ALL household contacts:**
- Household with **child <4 yrs** not fully Hib immunized
- Household with **infant <12 mo** not completed primary Hib series
- Household with **immunocompromised child <18 yrs**, regardless of vaccine status
- Always include the **index patient** unless treated with ceftriaxone/cefotaxime
-
- **Child care / preschool contacts:**
- Give prophylaxis if **≥2 cases in 60 days** + unimmunized/incompletely immunized children present

Hib meningitis Prophylaxis

- **Regimen (Rifampin):**
- ≥1 month: **20 mg/kg (max 600 mg) PO daily × 4 days**
- <1 month: **10 mg/kg PO daily × 4 days**
- Alternatives (ampicillin, cefaclor, TMP-SMX) **NOT effective**
-

- **Key Points:**
- Start **ASAP** after index case diagnosed
- Reduces nasopharyngeal carriage (≥95% eradication)
- Monitor all exposed children for illness (esp. twins—risk up to 25%)

Summary

- Acute bacterial meningitis remains a major cause of mortality and morbidity despite antibiotics
- Epidemiologic factors depend on availability of vaccination, crowding as well as availability of good health systems
- Host factors play a major role in brain damage need better therapies to modulate this
- Dexamthasone adjunct therapy now recommended for children and adults

Summary

- Outcome may be more guarded with subtle brain damage and decreased IQ
- Prevention is primary, vaccines for all three pathogens are now present
- In Jordan we have HIB for all children however Prevnar is available
- N meningitides for pilgrims and the military recruits
- Pneumoccocal vaccine needs to be included in the national program

Vaccine Effectiveness Against Pediatric Meningitis (U.S.)

- **Hib conjugate vaccine**
  - **95–100 % efficacy** against Hib meningitis in fully vaccinated children

- **Pneumococcal conjugate vaccines (PCV7/PCV13)**
  - Childhood PCVs reduced invasive pneumococcal meningitis by ~16,000 cases—part of >282,000 total IPD cases averted
  - Vaccine-type strain coverage: near **100 %** for 7 serotypes in infants; meta-analyses show ~**63–83 % effectiveness** against IPD, and high efficacy against meningitis in early studies

- **Meningococcal conjugate vaccines (MenACWY & MenB)**
  - MenACWY: ~**69 % effectiveness** in U.S. adolescents
  - MenB: **84–88 % immunogenicity** in adolescents; based on antibody response studies
  - New pentavalent MenACWY-B (Penbraya): recommended by ACIP in 2023 for ages 10–25 years

Dexamethasone use

- **Pathogen-Specific Evidence**
- **H. influenzae type b** (children ≥6 weeks): Steroids consistently shown to reduce hearing loss pmc.ncbi.nlm.nih.gov+10aafp.org+10uspharmacist.com+10 .
- **S. pneumoniae** (pneumococcal meningitis): Benefits in mortality/hearing outcomes; early use recommended emedicine.medscape.com+4publications.aap.org+4aafp.org +4.
- **Other bacteria** (Neisseria meningitidis, gram-negatives): Evidence weaker—discontinue once not confirmed .

Dexamethasone use

- **Clinical Integration**
- **Suspect pediatric bacterial meningitis** (≥ 6 weeks of age) → obtain blood cultures + LP.
- Start **empiric antibiotics** immediately.
- Administer **dexamethasone 0.15 mg/kg IV 10–20 min before or at antibiotic start**.
- Re-evaluate after CSF results:
  - Continue if confirmed **Hib** or **pneumococcus**.
  - Discontinue if CSF indicates another pathogen or aseptic meningitis.