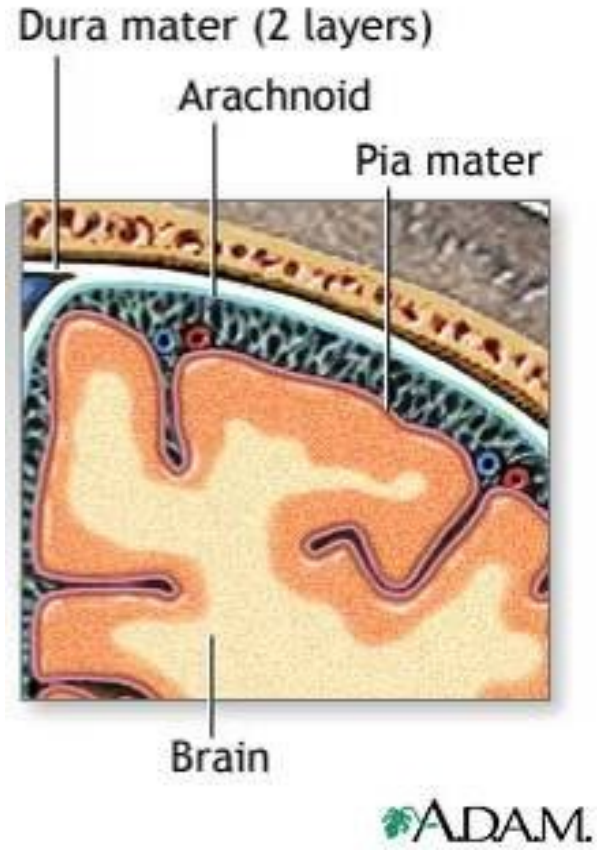
MENINGITIS IN CHILDREN

ASHIONO E. M

Definitions

- Meningitis – inflammation of the meninges
- Encephalitis – infection of the brain parenchyma
- Meningoencephalitis – inflammation of brain + meninges
- Aseptic meningitis – inflammation of meninges with sterile CSF



KENYA

- 390 cases (1.3% of all admissions) of whom 88% were <5 years old
- The apparent minimum annual incidence in children younger than 5 years of age increased from 120 to 202 per 100 000 between 1995 and 2000 ($P < 0.001$).
- Increasing the lumbar punctures performed by including prostrated or convulsing children significantly increased the number of cases detected ($P < 0.005$).
- The most common organisms in infants <3 months were streptococci and Enterobacteriaceae . *Streptococcus pneumoniae* (43.1%) and *Haemophilus influenzae* (41.9%) were predominant in the postneonatal period.

- The overall mortality was 30.1%, and 23.5% of survivors developed neurologic sequelae.
- Chloramphenicol resistance of *H. influenzae* rose from 8% in 1994 to 80% in 2000 ($P < 0.0001$) accompanied by an apparent increase in mortality.
- A short history, impaired consciousness and hypoglycemia were associated with death.
- Prolonged coma and low cerebrospinal fluid glucose were associated with neurologic sequelae.

Acute bacterial meningitis in children admitted to a rural Kenyan hospital: increasing antibiotic resistance and outcome MWANGI, ISAIAH MTROPPAEDS; BERKLEY, JAMES MRCP; LOWE, BRETT MPHIL; PESHU, NORBERT MPH; MARSH, KEVIN FRCP; NEWTON, CHARLES R. J. C. MD The Pediatric Infectious Disease Journal:

November 2002 - Volume 21 - Issue 11 - pp 1042-1048

KNH,NEONATES

- The prevalence of meningitis amongst cases of suspected sepsis was 17.9%.
- The male:female ratio was 1.5:1 mean birth weight 2116.7 grams (1682.2-2551.2) mean gestational age 35.7 weeks (32.6-38.8) and the mean postnatal age was 4.1 days (2.7-5.4) with none of the parameters being significantly different from those without meningitis.
- Feed intolerance and lethargy were the most common clinical features, present in 73.3% and 60% of patients with meningitis respectively.
- Neonates with meningitis had a higher mean CSF protein value (2.67 g/L vs 1.97 g/L, p=0.367) and a significantly higher mean CSF white cell count (21 cells/mL vs 7 cells/mL, p=0.001).
- The most common aetiological agents were Escherichia coli (46.7%). Group B. Streptococci (26.7%) and Klebsiella pneumoniae (13.3%).

- Most blood and CSF isolates were resistant to ampicillin and gentamicin but showed good in-vitro sensitivities to amikacin, cefuroxime and the third generation cephalosporins (ceftriaxone, ceftazidime and cefotaxime).
- Blood cultures were positive in only 53.3% of neonates with meningitis.
- Resistance to the commonly employed first-line antibiotics (penicillin and gentamicin) is high and a change of empirical antibiotic use for neonates with suspected sepsis is recommended.

Neonatal bacterial meningitis at the newborn unit of Kenyatta National Hospital. East Afr Med J. 2003 Sep;80(9):456-62

Laving AM, Musoke RN, Wasunna AO, Revathi G

Department of Paediatrics and Child Health, College of Health Sciences, University of Nairobi, PO Box 19676, Nairobi, Kenya

TRANSMISSION

- Droplet transmission of bacteria from person to person
- Close and prolonged contact e.g sneezing,coughing
- Incubation period 2-10 days

Routes of infection

- Nasopharynx
- Bloodstream
- Direct spread(skull fracture,meningo/encephalocele
- Middle ear infection
- Infected VP shunts
- Congenital defects
- Sinusitis

TYPES

- Bacterial
- Viral
- Fungal
- Parasitic
- Non infectious

Bacterial meningitis - Organisms

- Neonates
  - Most caused by Group B *Streptococci*
  - *S.AureusE coli,* enterococci, *Klebsiella, Enterobacter, Samonella, Serratia, Listeria*
- Older infants and children
  - *Neisseria meningitidis, S. pneumoniae, tuberculosis, H. influenzae*

NEONATES

- 0-7 days days - group B Streptococcus (GBS), E. coli, other enteric bacilli, and L. monocytogenes. Uncommon pathogens include other streptococci, non-typeable Haemophilus influenzae, Neisseria meningitidis, and Streptococcus pneumoniae.
- 7 days or older - antimicrobial-resistant gram-negative organisms must be considered in addition to above.
- Hospitalized neonates seven days of age or older - gram-positive organisms must be considered in addition to antimicrobial resistant gram-negative organisms, GBS, E. coli, and L. monocytogenes.

HOST PATHOGEN INTERACTION

- Variety of factors including preceding viral infections, inhalation of dry dusty air, or exposure to passive smoking have been associated with invasive disease
- Meningococcus is able to adhere to non-ciliated epithelial cells through a number of adhesion factors, including pili

- Bacterium avoids host immunological mechanisms in the nasopharynx by:
  - production of IgA protease
  - production of factors which inhibit ciliary activity
  - possession of a polysaccharide capsule which promotes adherence and inhibits opsonophagocytosis
  - variation in expression or structure of a variety of surface antigens, including proteins and endotoxin *e.g In group B meningococci, the polysaccharide structure is nonimmunogenic, because of structural similarity with the human neural cell adhesion molecule (NCAM)*

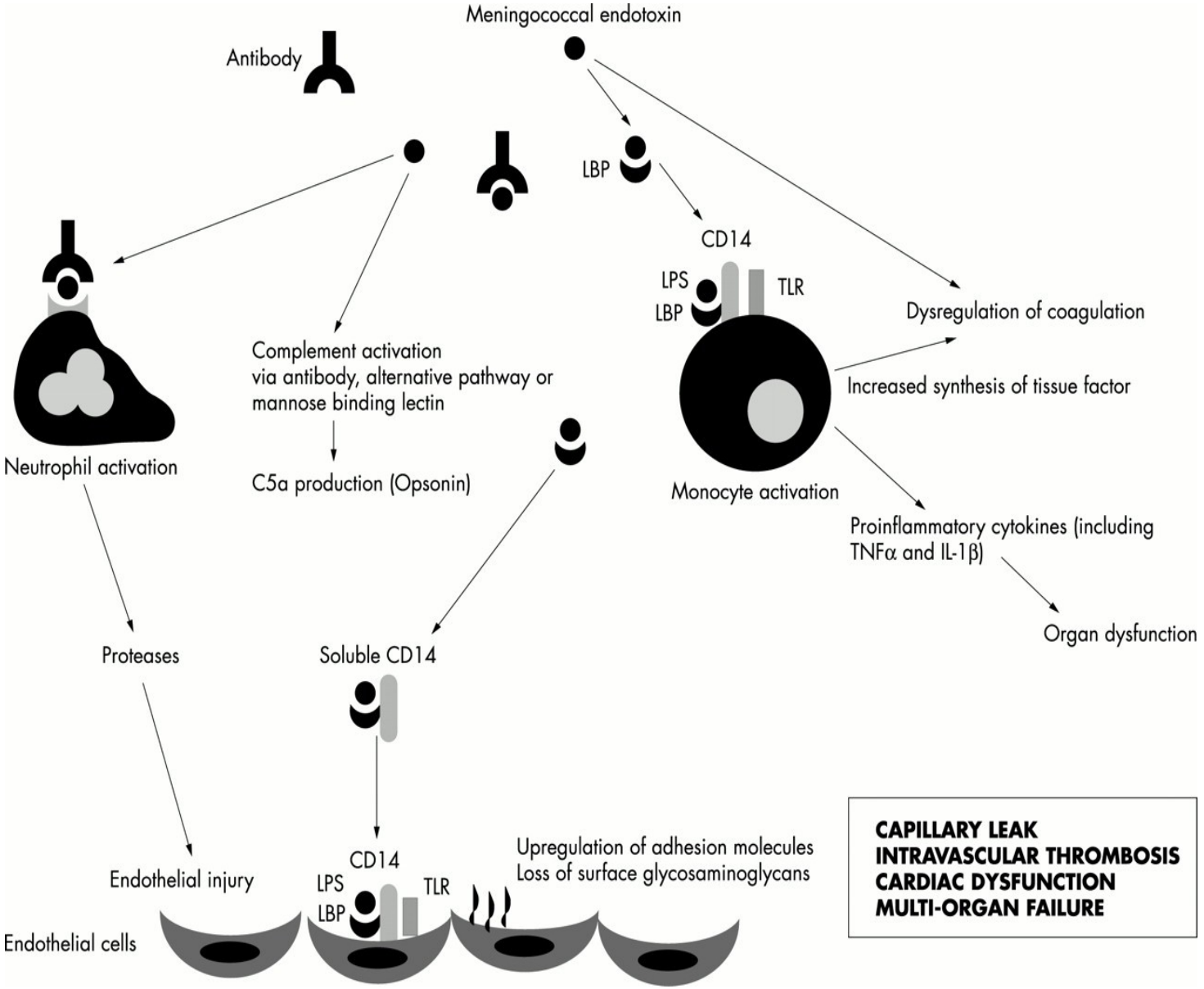
Host factors

- Passive immunity
- Acquired immunity
- Complement pathway:Classical,alternate,MBL pathways- *Individuals deficient in terminal components of the complement pathway or properdin,suffer recurrent infection.Individuals with mutations in the mannose binding lectin gene have an increased risk of meningococcal disease but appear less likely to suffer recurrent infections once antibodies have developed.*

PATHOGENESIS OF BACTERIAL MENINGITIS

- Entry of organism through BBB
- Release of cell wall and membrane products
- Outpouring of polymorphs and fibrin
- Cytokines and chemokines
- Inflammatory mediators
- Inflammed meninges covered with exudate(most marked in pneumoccocal meningitis)

The inflammatory cascade in meningococcal septicaemia.



Pathan N et al. Arch Dis Child 2003;88:601-607

MICROVASCULAR INJURY IN MENINGOCOCCAL SEPSIS

- The complex physiology of meningococcal sepsis is largely explained by four basic processes affecting the microvasculature:

  (1) Increased vascular permeability

  (2) Pathological vasoconstriction and vasodilatation

  (3) Loss of thromboresistance and intravascular coagulation

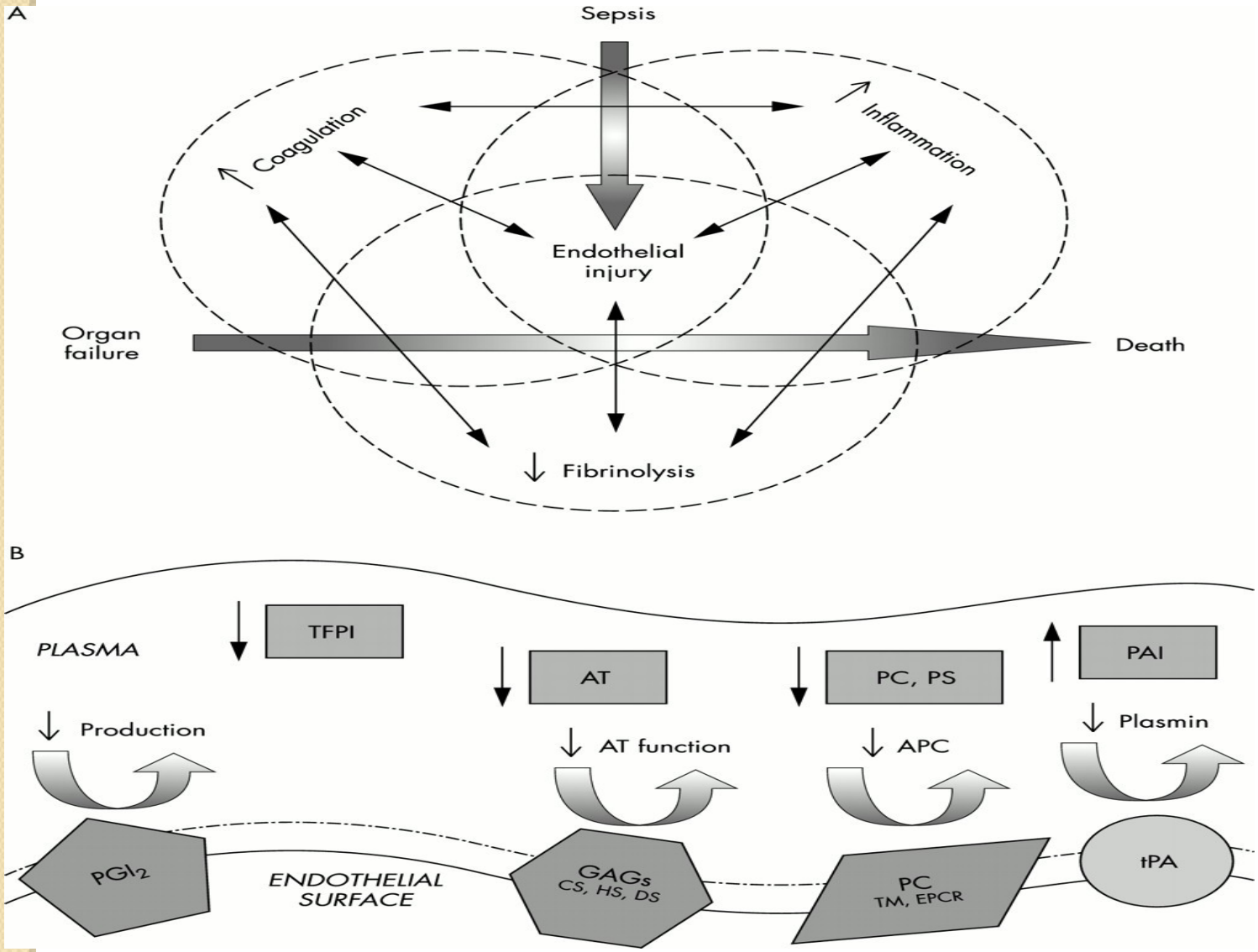
  (4) Profound myocardial dysfunction.

- These events are largely responsible for the development of shock and multiorgan failure.

Increased vascular permeability and the capillary leak syndrome

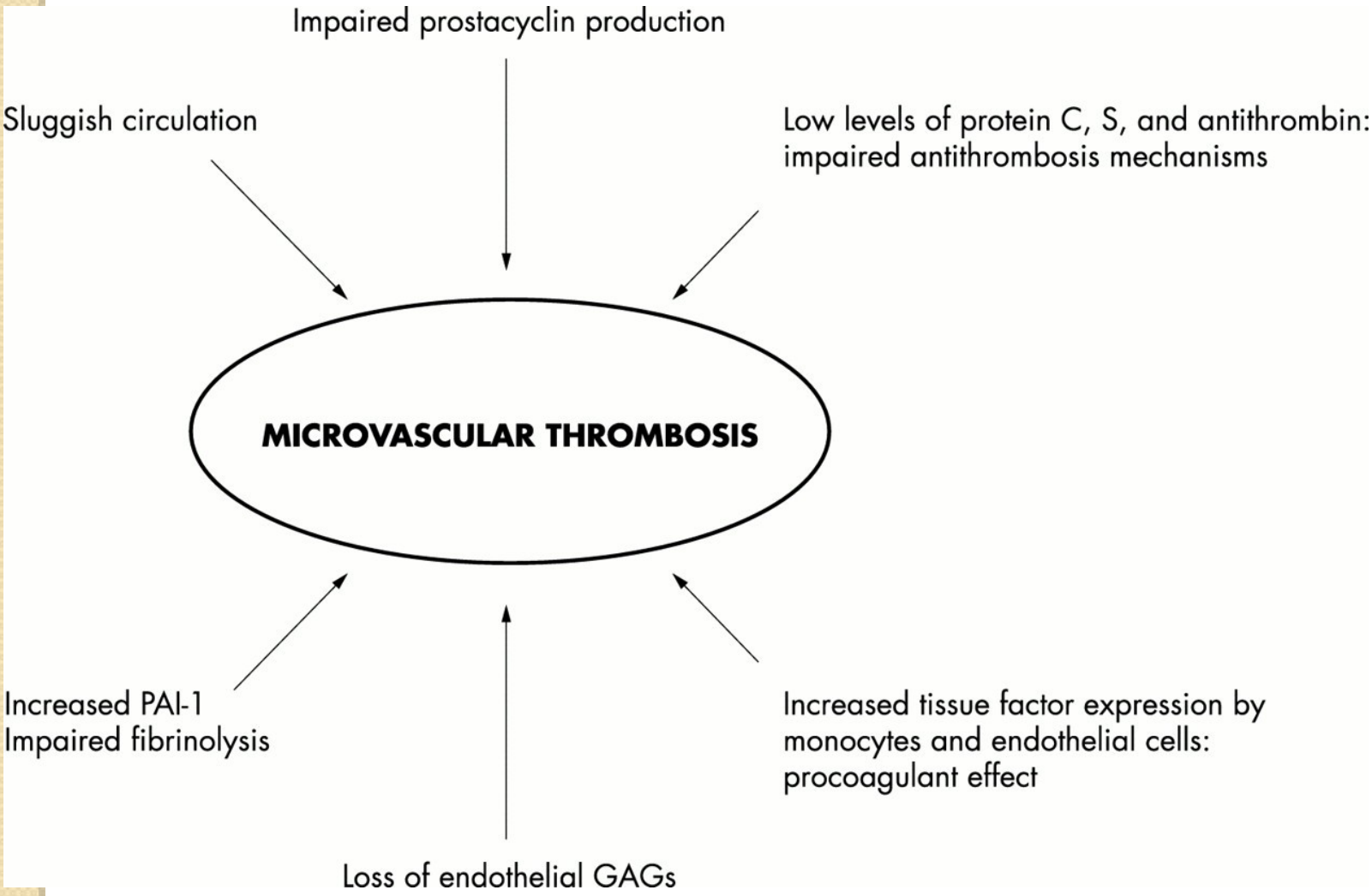
- Hypovolemia, a direct result of a gross increase in vascular permeability, appears to be the most important early event leading to shock
- Increased capillary leak due to:
  - Increased inflammation
  - Enzymatic degradation of endothelial surface proteins
  - loss of the surface endothelial glycosaminoglycans
  - Leads to loss of albumin,fluids and electolytes

(A) The inflammatory, coagulation, and fibrinolytic pathways are linked at many levels, leading to organ failure and eventually death.



Pathan N et al. Arch Dis Child 2003;88:601-607

Factors involved in intravascular thrombosis and purpura fulminans.

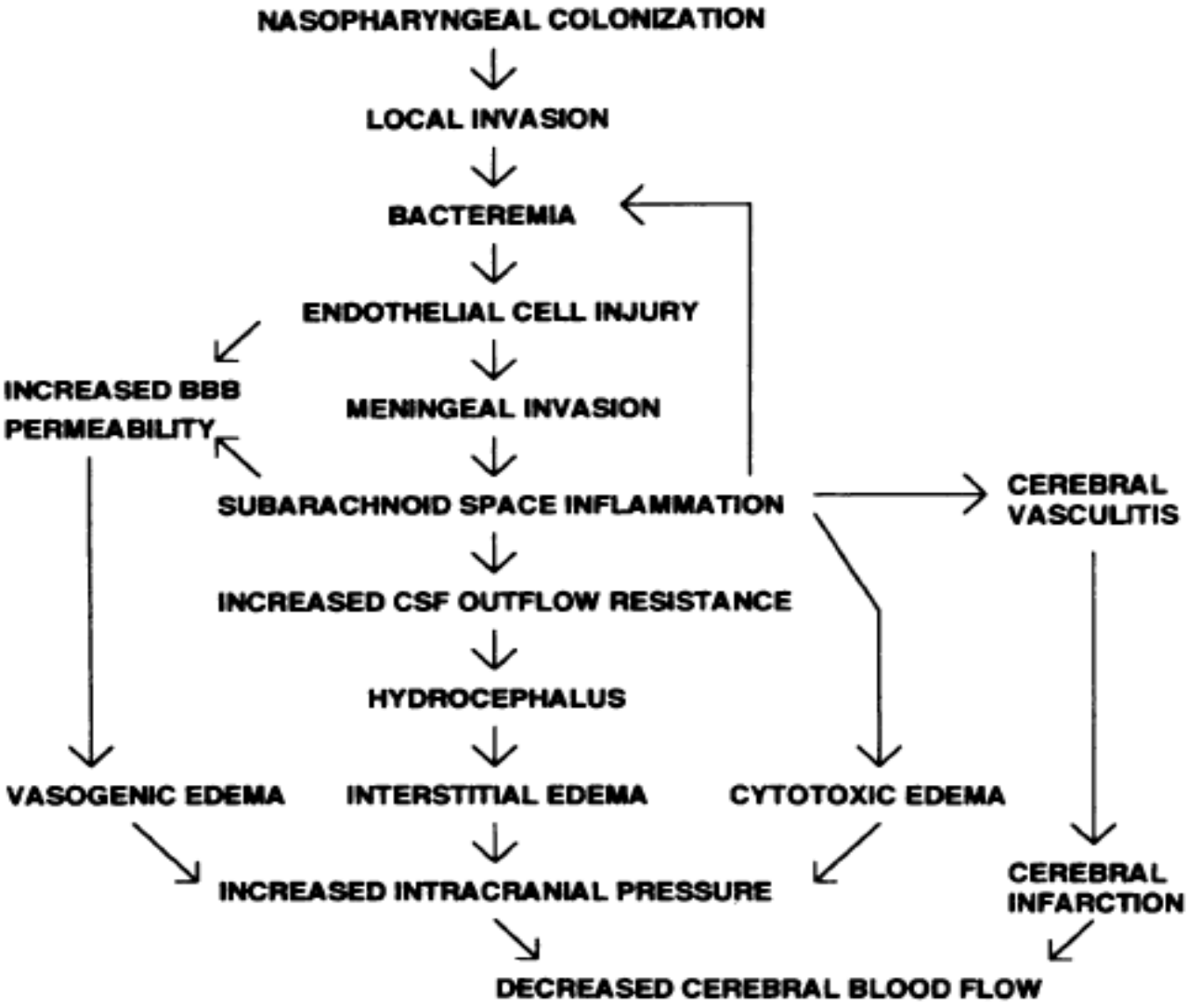


Pathan N et al. Arch Dis Child 2003;88:601-607

NEUROLOGIC INJURY

- Direct bacterial toxicity
- Indirect inflammatory processes such as cytokine release, neutrophil activation, with resultant vasculitis, and cellular oedema
- Cerebral oedema may be caused by increased secretion of CSF, diminished reabsorption of CSF, and breakdown of the blood-brain barrier

Pathogenesis and pathophysiology of bacterial meningitis



PATHOPHYSIOLOGY

- Meningeal irritation signs:Inflammation of the spinal nerves and roots
- Hydrocephalus:Adhesive thickening of the arachinoid in basal cistern or fibrosis of aqueduct or foramina of Luschka or Magendie
- Cerebral atrophy: Thrombosis of small cortical veins resulting in necrosis of the cerebral cortex

- Seizures: Depolarization of neuronal membranes as a result of cellular electrolyte imbalance
- Hypoglycorhachia: Decreased transport of glucose across the inflammed choroid plexus and increased usage by host

Symptoms and Signs of Bacterial Meningitis

Rapid Onset (25%) hospitalized < 24h

Respiratory Symptoms days – weeks

Headache 90%

Fever >90%

Δ consciousness 80%

Vomiting – 30%

Seizures – 30%

Petechiae/purpura 50%

Meningismus 85%

Focal neurosigns 25%

Ocular palsies – 10%

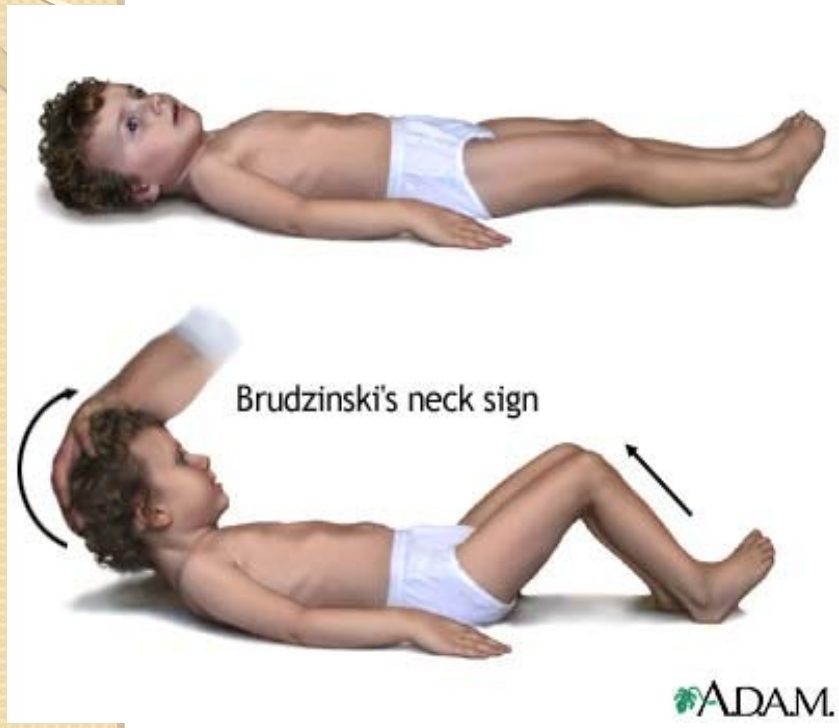
Hemiparesis

Myalgias 20%

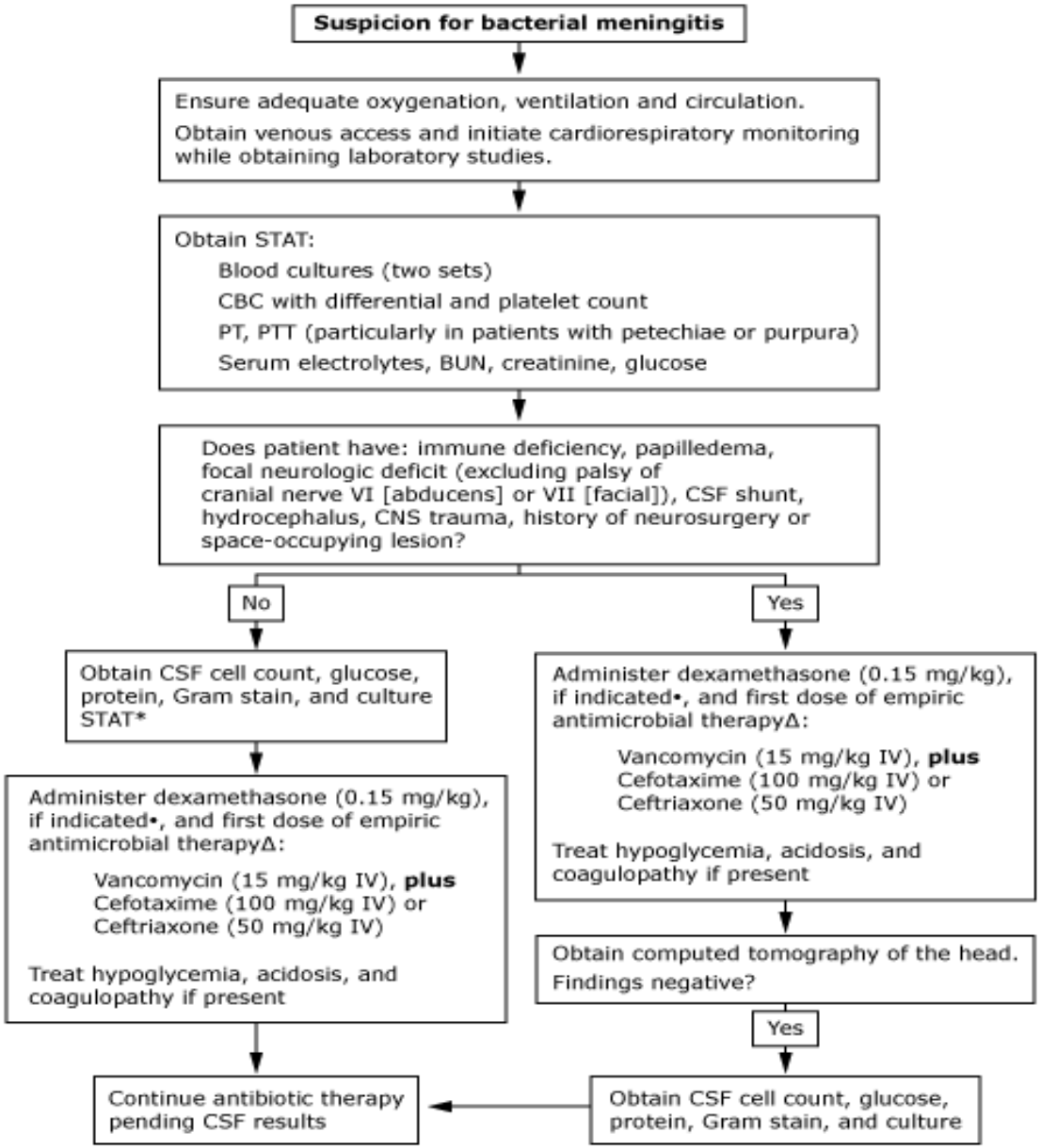
(meningo.)

Papilledema 1%

Clinical signs of meningeal irritation



Management algorithm for infants (>1 month) and children with suspected bacterial meningitis



VIRAL MENINGITIS

- Comprises most aseptic meningitic syndromes.
- Agents include:
  - Enterovirus(Polio,Echovirus,Coxsackievirus
  - Herpesvirus(HSV,EBV,Varicella Z)
  - Paramyxovirus(Mumps,Measles)
  - Togavirus(Rubella)
  - Rhabdovirus9Rabies)
  - Retrovirus(HIV)

FUNGAL MENINGITIS

- Rare in healthy children
- Higher risk in those with HIV/AIDS,immunodeficiency/immunosuppression syndromes
- Most common agents are Cryptococcus neoformans,Candida,H capsulatum

PARASITIC MENINGITIS

- Infection with free living amoeba is an infrequent but often life threatening human illness
- More common in developing countries,usually caused by parasite found in contaminated water,food and soil
- Most common causative agents are: free living amoeba(Acanthamoeba,Balamuthia,Naegleria)Helminthic eosinophilic meningitis

NON-INFECTIOUS MENINGITIS

- SLE
- Rare causes include exposure to certain meds such as
  - Immune globulin
  - Levamisole
  - Metronidazole
  - MMR
  - NSAIDS

TBM

- Complication of childhood TB and common cause of prolonged morbidity,handicap and death
- Children below 5yrs of age at risk

C/F

- Always secondary to primary TB
- First Phase: prodromal phase, lasting two to three weeks
- Vague symptoms
  - Child dull,irritable,restless,or drowsy
  - Anorexia & vomiting may be present
  - Older child may c/o headache
  - Often preceding history of illness with incomplete recovery
  - low-grade fever
  - personality change.

Second phase: meningitic phase

- Confusion,drowsy,neck stiffness and rigidity, and protracted headache
- Vomiting,lethargy
- Kerning and Brudzinski sign may be positive,bulging of ant fontanelle
- Twitching of muscles,convulsions,fever
- Strabismus,nystagmus and papilloedema may be present
- Fundoscopy: Choroidal TB may be seen
- Varying degrees of cranial nerve and long-tract signs

Terminal phase: paralytic phase

- Confusion gives way to stupor and coma,opisthotonus position
- Multiple focal paresis
- CN palsies present
- High grade fever persists
- For the majority of untreated patients, death ensues within five to eight weeks of the onset of illness

CLINICAL STAGES

Useful for prognosis and therapy

- Stage I patients are lucid with no focal neurologic signs or evidence of hydrocephalus.
- Stage II patients exhibit lethargy, confusion; may have mild focal signs, such as cranial nerve palsy or hemiparesis.
- Stage III represents advanced illness with delirium, stupor, coma, seizures, multiple cranial nerve palsies, and/or dense hemiplegia.

Diagnostic accuracy of physical findings in adults with suspected meningitis*

297 patients, 80 (27%) with “meningitis”

18/80 microbiologic dx; 3 bacterial

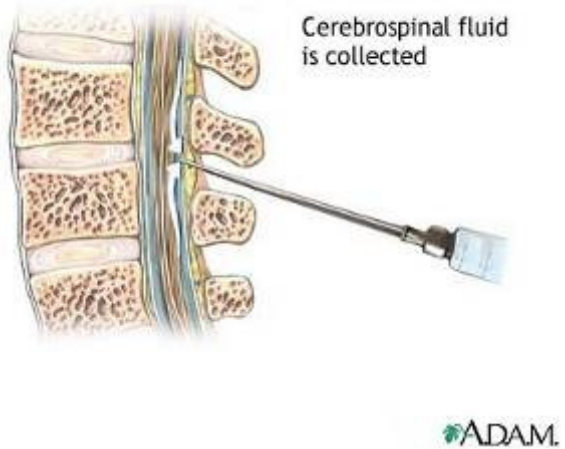
Kernig’s, Brudzinskis signs: sens = 5%, NPV = 72%

Nuchal rigidity sens = 30% NPV = 73%

CSF wbc >1000 sens = 100% NPV = 100%

*Thomas KE, et al. Clin Infect Dis 2002; 35:46-52.

Diagnosis – lumbar puncture



- Contraindications:
  - Respiratory distress (positioning)
  - ↑ ICP reported to increase risk of herniation
  - Cellulitis at area of tap
  - Bleeding disorder

CSF evaluation

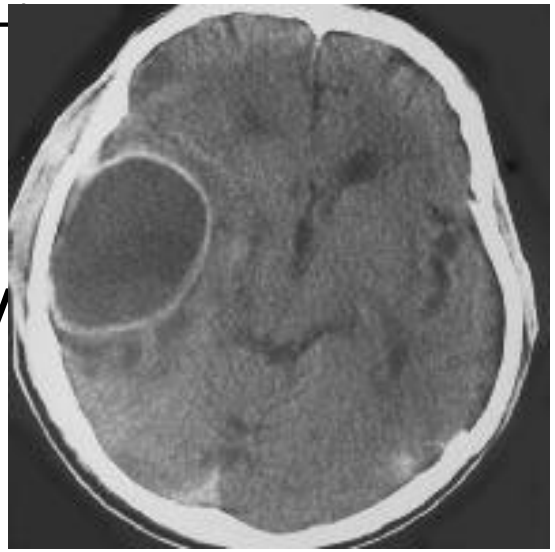
Condition	WBC	Protein (mg/dL)	Glucose (mg/dL)
Normal	<7, lymphs mainly	5-45	>50
Bacterial, acute	100 – 60K PMN's	100-500	Low
Bacterial, part rx'd	1 – 10,000	100+	Low to normal
TB	10 – 500	100-500	<50
Fungal	25 – 500	25-500	<50
Viral	<1000	50-100	Normal

Who has bacterial meningitis and who needs an LP? – consider 100 cases of meningitis

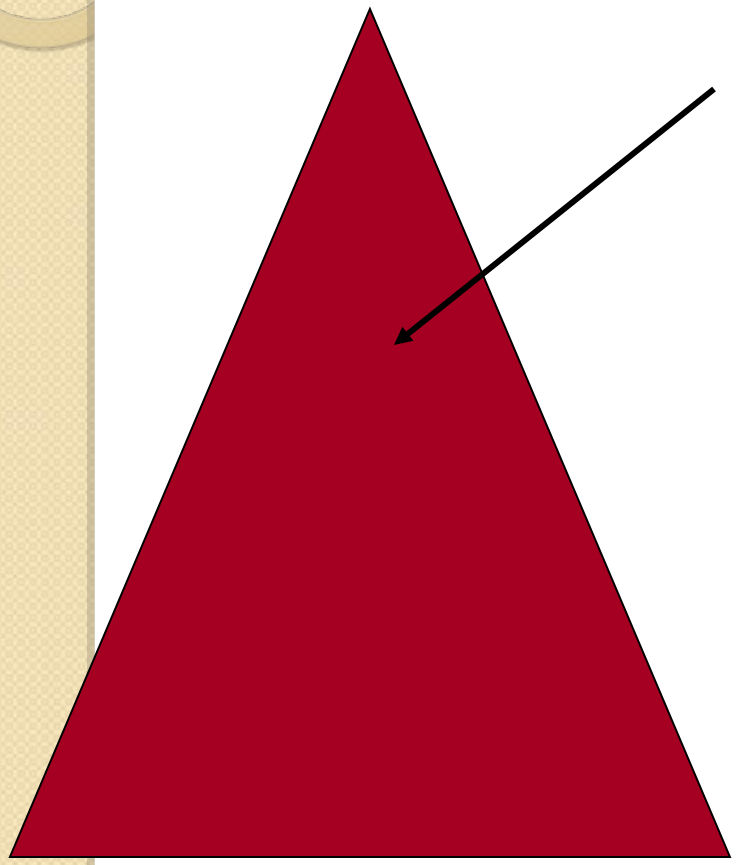
	Clinical signs in a febrile child	Able to detect	Missed	Number over-diagnosed
1	Bulging fontanelle / Stiff neck	40	60	110
2	Signs in 1 or fits aged <6m or fits aged > 6yrs	60	40	215
3	Signs in 1 or 2 or partial or focal convulsions	70	30	495
4	Signs in 1 or 2 or 3 or reduced consciousness	80	20	915

So what is a sensible rule for LP?

- At a minimum, if you want to avoid missing meningitis (and deaths and handicap from it), and avoid wasting antibiotics, at least LP those with history of fever and one of:
  - Bulging fontanelle
  - Stiff neck
  - Fits if age <6 months or > 6 y
  - Partial or focal fits
  - Reduced consciousness

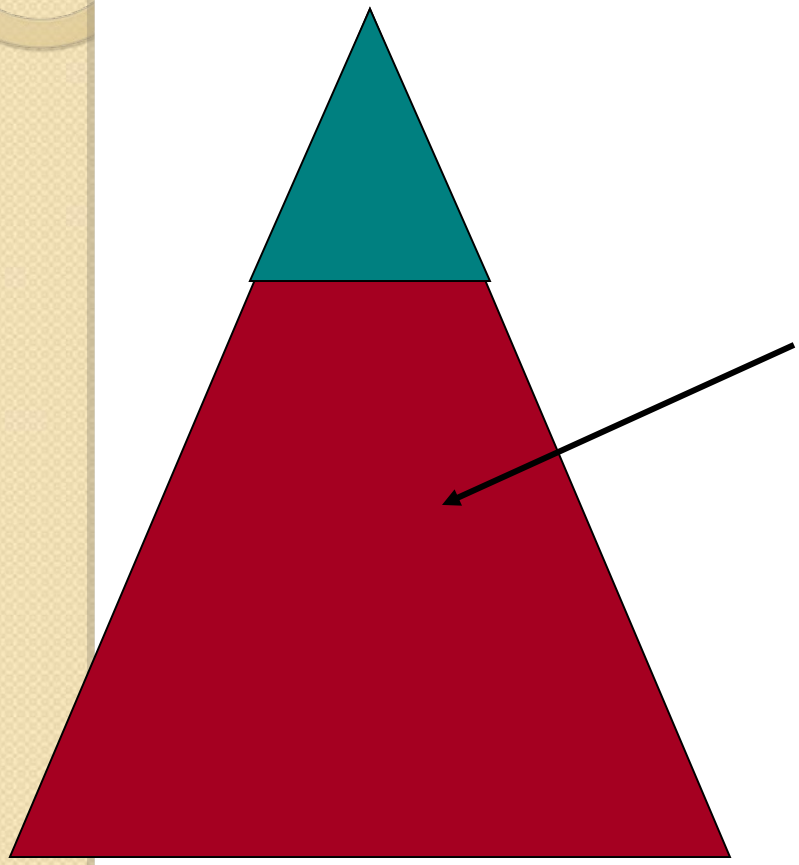


Value of LP findings – Acute bacterial meningitis.



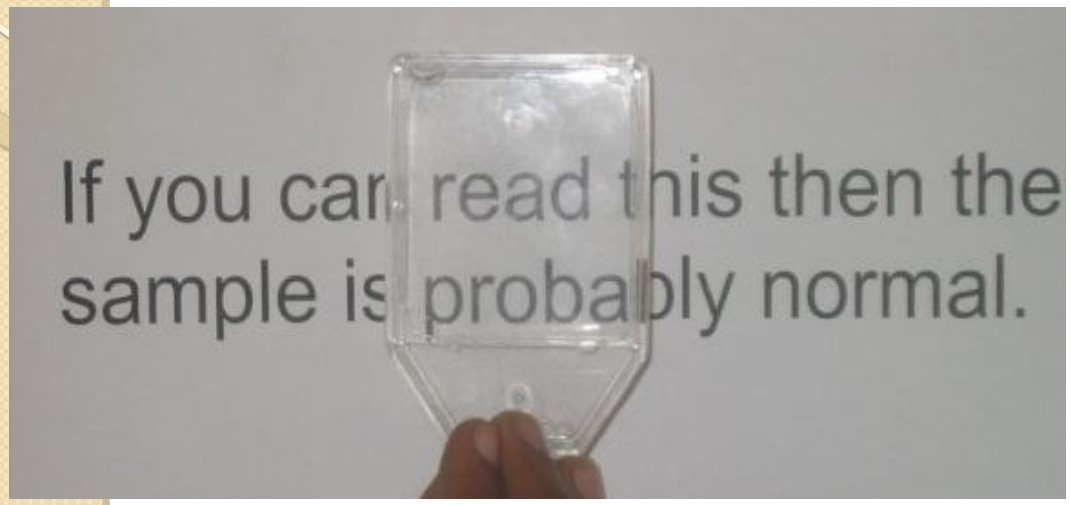
All the true acute bacterial meningitis cases

Bedside assessment alone is very helpful.



75% of acute bacterial meningitis cases can be detected by examining for CSF cloudiness or turbidity at the bedside.

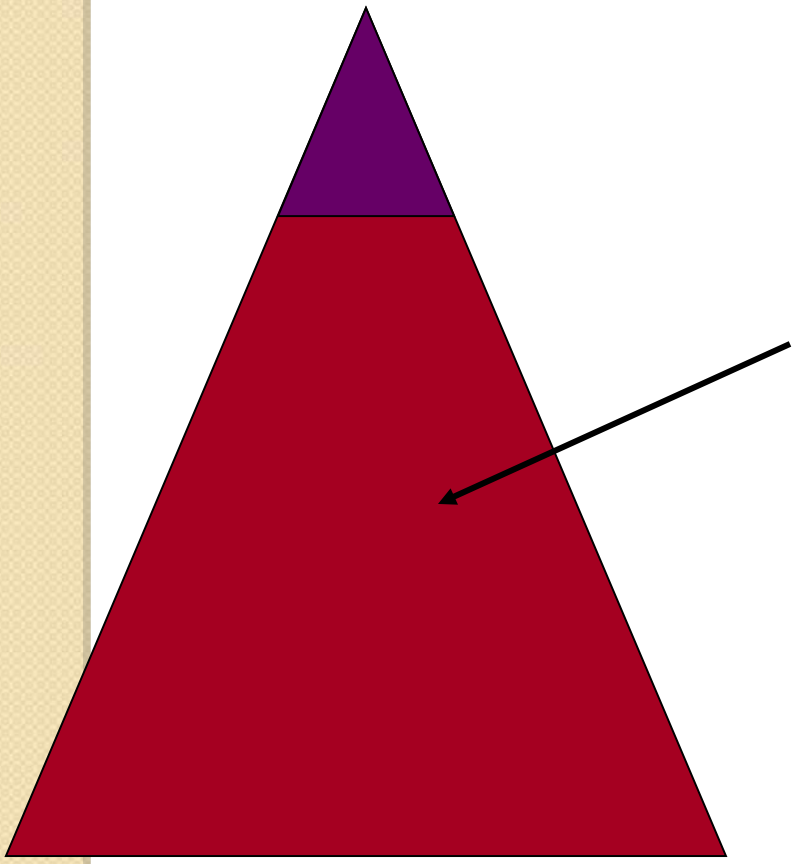
CSF Cloudiness / Turbidity



A simple test of CSF turbidity is to see if normal print can be read easily through the sample – CSF should be crystal clear.

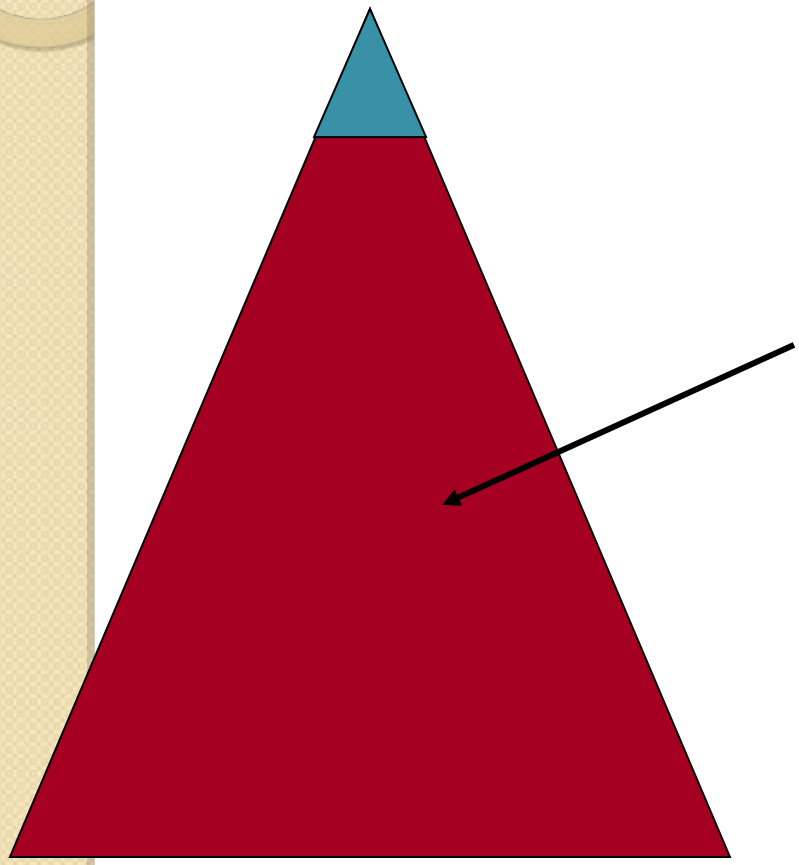
Cloudiness usually appears at CSF WBC counts > 200×10^6 Wbc per L

CSF culture is great but if it is not available a microscope will provide nearly all you need to know.



82% of acute bacterial meningitis cases can be detected by either turbidity or a CSF white cell count and using a cut-off of >50 Wbc per µL. (>50 x 10^6 Wbc per L)

CSF microscopy, blood and CSF glucose measures are highly sensitive.



96% of acute bacterial meningitis cases can be detected by turbidity, a CSF white cell count of >50 Wbc per µL (>50 x 10^6 Wbc per L) or a CSF glucose to Blood glucose ratio <0.1*

** Books suggest a ratio of ~0.6, this is much too high to be useful*

MICROSCOPY – GRAM STAIN

- Absence of organisms on Gram stain does not exclude the diagnosis .
- The probability of visualizing bacteria depends upon the number of organisms present and is increased by cytocentrifugation
- An organism is visualized on CSF Gram stain in approximately 90 percent of children with pneumococcal meningitis and 80 percent of children with meningococcal meningitis.
- In contrast, Gram stain is positive in only one-half of patients with gram-negative bacillary meningitis and one-third of patients with listeria meningitis

MICROSCOPY

- 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
- Gram-positive rods and coccobacilli suggest L. monocytogenes

LP changes after antibiotics.

- Prior antibiotic use reduces the sensitivity of CSF gram stain by 20% and CSF culture by 30%.
- It takes 24-36 hours of therapy before >90% of CSF cultures will be sterile.
- It takes 2-3 days of therapy to change the WBC cell count of CSF in true bacterial meningitis.
- ***Prior treatment is no excuse for not doing an LP!***

LATEX AGGLUTINATION

- Commercial kits utilizing latex beads coated with antibodies to meningococcal capsular antigens are available for use in body fluids other than blood (eg, CSF and urine)
- Detect agglutination of five capsular types: A, B, C, Y, and W135.
- The sensitivity for serogroup B is low, and false negative results can occur

POLYMERASE CHAIN REACTION

- Detects small quantities of bacterial DNA
- Has the potential to be an important tool in the rapid diagnosis of meningococcal infection.
- Advantages compared to culture for the diagnosis of meningococcal infection include:
  - It can establish the diagnosis more rapidly
  - Since viable bacteria are not required, sensitivity is not affected by prior antibiotic administration
  - It can rapidly type strains, a useful adjunct in situations that appear to be an epidemic in evolution
  - Multiplex PCR permits simultaneous testing for meningococcal, pneumococcal, and Haemophilus influenzae infection

PCR Cont:

- Also useful in diagnosis of TBM and viral meningitis
- Methods for the rapid detection of M. tuberculosis in CSF include the nucleic acid-based amplification test (NAAT) that relies upon PCR
- Poor sensitivity,largely attributed to the difference in sample volume between PCR (typically around 50 microL) and culture (several mL)

OTHER TESTS

- Serum C-reactive protein - not a reliable indicator of severe infection
- In retrospective cohorts, elevated serum procalcitonin (>0.5 ng/mL) appears to be helpful in distinguishing bacterial from viral meningitis
- Presence of tumor necrosis factor may distinguish bacterial from viral meningitis
- Presence of IL-1 or IL-10 also may correlate with meningitis, but whether these indicators are sensitive and specific enough to accelerate the diagnosis remains to be determined

But the lab needs….

- Specimens before treatment ideally
- CSF must be processed within 1 hour of collection
  - CSF cannot be put in a fridge
  - Only put CSF in an incubator if the temperature is < 15^0C and it cannot be taken to the lab quickly.

TREATMENT

- Empiric regimen for infants and children older than 1 month with bacterial meningitis include coverage for antibiotic-resistant S. pneumoniae, N. meningitidis, and Hib
- Cefotaxime (300 mg/kg/d[IV], maximum dose 12 g/day, in 3 or 4 divided doses) or
- Ceftriaxone (100 mg/kg/d IV, maximum dose 4 g/day in 1 or 2 divided doses) plus
- Vancomycin (60 mg/kg per day IV, maximum dose 2 g/day, in 4 divided doses)

DURATION OF THERAPY

- S. pneumoniae — 10 to 14 days
- N. meningitidis — 5 to 7 days
- Hib — 7 to 10 days
- L. monocytogenes — 14 to 21 days
- Gram-negative bacilli — 3 weeks or a minimum of 2 weeks beyond the first sterile culture, whichever is longer

Pneumococcal resistance

- *Strep pneumococcus* - most common cause of invasive bacterial infections in children >2 months old
- Incidence of PCN-, cefotaxime- & ceftriaxone-nonsusceptible isolates has ↑'d to ~40%
- Strains resistant to PCN, cephalosporins, and other β-lactam antibiotics often resistant to trimethoprim-sulfamethoxazole (Bactrim™, Septra™), erythromycin, chloramphenicol, tetracycline

Mechanism of resistance

- PCN-binding proteins synthesize peptidoglycan for new cell wall formation
- PCN, cephalosporins, and other β-lactam antibiotics kill *S pneumoniae* by binding irreversibly to PCN-binding proteins located in the bacterial cell wall
- Chromosomal changes can cause the binding affinity for the β-lactam antibiotics to decrease

Kilifi study

TABLE 4. Antimicrobial resistance patterns of common cerebrospinal fluid isolates

Patient Age (mo)	Resistance to	No./Total Isolates	
<3 mo	Penicillin or gentamicin		
	Haemophilus influenzae	2/8	(25)*
	Streptococcus pneumoniae	6/21	(29)
	Other organisms	1/25	(4)
	All	9/54	(17)
>3 mo	Penicillin or chloramphenicol		
	H. influenzae	16/60	(27)
	S. pneumoniae	0/60	(0)
	Other organisms	0/17	(0)
	All	16/137	(12)
All ages	Cefotaxamine		
	H. influenzae	1/68	(1.5)
	S. pneumoniae	0/81	(0)
	Other organisms	2/42	(5)
	All	3/191	(1.6)

* Numbers in parentheses, percent.

Other antibiotics in pneumococcal meningitis (resistant)

- Meropenem
  - Carbapenem
  - 120 mg/kg/day ÷ Q 8 h
  - ↑ seizure incidence, ∴ not generally used in meningitis
  - Resistance reported
- Rifampin
  - 20 mg/kg/day ÷ Q 12
  - Not a solo agent
  - Slowly bactericidal

Age Group	Common Bacterial Pathogens	Initial Antibiotic Regimen
Newborn	Group B *Streptococcus* *Escherichia coli* *Klebsiella pneumoniae* *Listeria monocytogenes* *Enterococcus* sp. *Salmonella* sp.	Ampicillin plus aminoglycoside or cefotaxime
4–12 weeks	Group B *Streptococcus* *Escherichia coli** *Listeria monocytogenes* *Haemophilus influenzae* *Streptococcus pneumoniae* *Neisseria meningitidis*	Ampicillin plus either cefotaxime or ceftriaxone
12 weeks and older	*Haemophilus influenzae* *Streptococcus pneumoniae* *Neisseria meningitidis*	Ceftriaxone or cefotaxmine (ampicillin and chloramphenicol is a suitable alternative)

* Gram-negative enteric bacilli can cause disease in low birth weight preterm infants in this age group.

Dexamethasone use in meningitis

- Consider if H flu & S pneumo meningitis & > 6 wks old 0.6 mg/kg/day ÷ Q 6h x 2d
- ↓ local synthesis of TNF-α, IL-1, PAF & prostaglandins resulting in ↓ BBB permeability, ↓ meningeal irritation
- Debate if it ↓ incidence of hearing loss
- If used, needs to be given shortly before or at the time of antibiotic administration – within 1hr
- May adversely affect the penetration of antibiotics into CSF

Meningococcemia - Treatment

- Antibitotic resistance rare
- Antibitotics:
  - PCN
  - Cefotaxime or Ceftriaxone
- Patient should get rifampin prior to discharge

Meningococcemia - Prophylaxis

- No randomized controlled trials of effectiveness
- Treat within 24 hours of exposure
- Vaccinate affected population, if outbreak

Meningococcemia - Prophylaxis

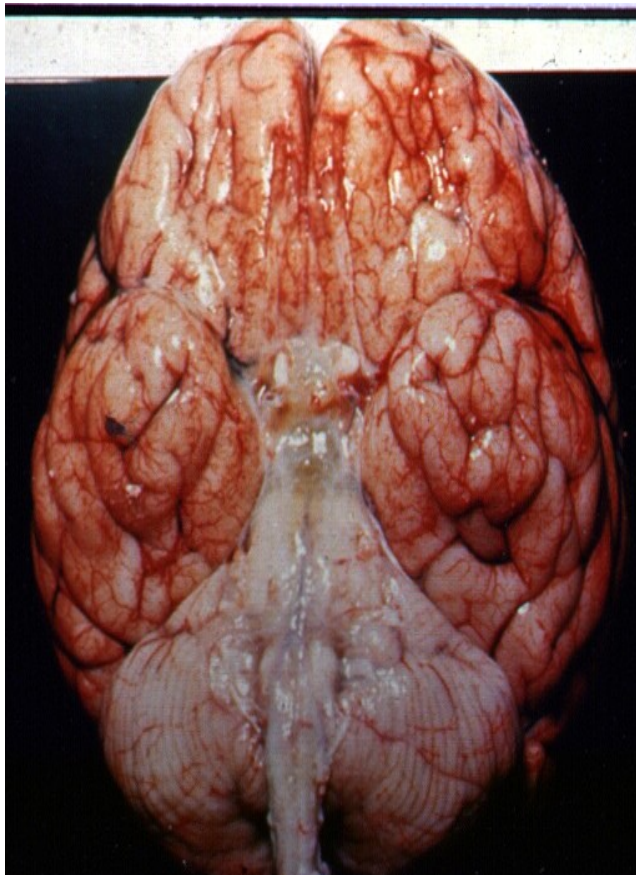
- Rifampin
  - Urine, tears, soft contact lenses orange; OCP's ineffective
  - <1 mo 5 mg/kg PO Q 12 x 2 days
  - >1 mo 10 mg/kg (max 600 mg) PO Q 12 x 2 days
- Ceftriaxone
  - ≤12 y 125 mg IM x 1 dose
  - >12 y 250 mg IM x 1 dose
- Ciprofloxacin
  - ≥18 y 500 mg PO x 1 dose

Meningococcal meningitis - Outcomes

- Substantial morbidity: 11% - 9% of survivors have sequelae
  - Neurologic disability
  - Limb loss
  - Hearing loss
- 10% case-fatality ratio for meningococcal sepsis
- 1% mortality if meningitis alone

TB meningitis

- CSF:
  - Profoundly low glucose
  - High protein
  - Acid-fast bacteria (AFB stain)
  - PCR
- Steroids + anti TBs



Viral meningitis - Treatment

- Supportive
- No antibiotics
- Analgesia
- Fever control
- Often feel better after LP
- No isolation - Standard precautions

Viral meningitis - Outcomes

- Adverse outcomes rare
- Infants <1 year have higher incidence of speech & language delay

Herpes simplex 1 encephalitis

- Symptoms
  - Depressed level of consciousness
  - Blood tinged CSF
  - Temporal lobe focus on CT scan or EEG
  - + PCR
  - Neonates typically will have cutaneous vessicles
- Treatment - IV acyclovir, <12 years, 60 mg/kg/d, ≥ 12 years old, 30 mg/kg/d TID for 14-21 days

Vaccines

- Streptococcus pneumoniae - conjugate vaccines and Pneumococcal polysaccharide vaccines in children
- Neisseria meningitidis - Meningococcal vaccines - Immunizations for children age 7 to 18 years
- Haemophilus influenzae type b (Hib) – Penta valent vaccine

Meningitis - Acute complications

- Hydrocephalus
- Subdural effusion or empyema ~30%
- Stroke
- Abscess
- Dural sinus thrombophlebitis

REFERENCES

- **Nelson’s textbook of pediatrics 21st edition**
- ***Up to date***

THANK YOU!