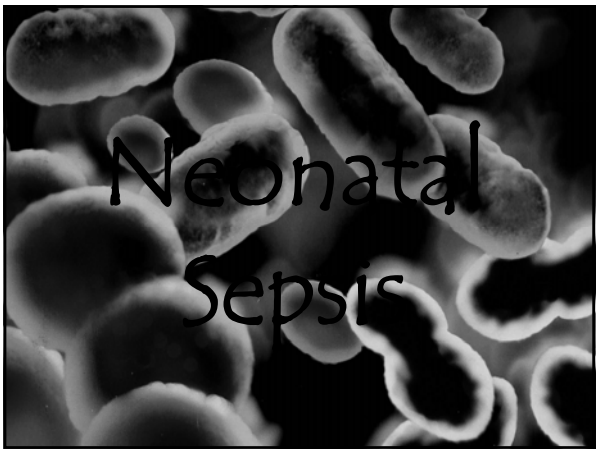
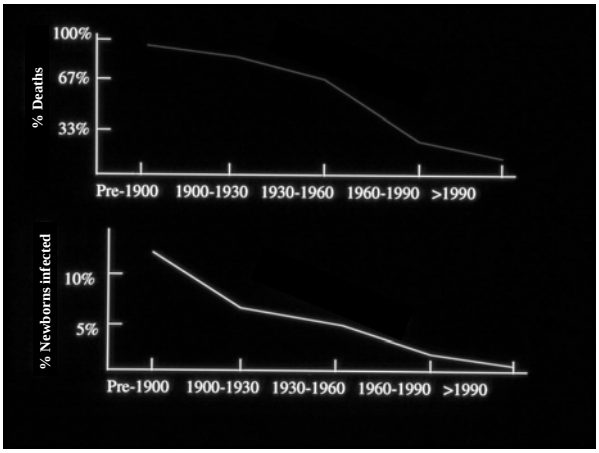
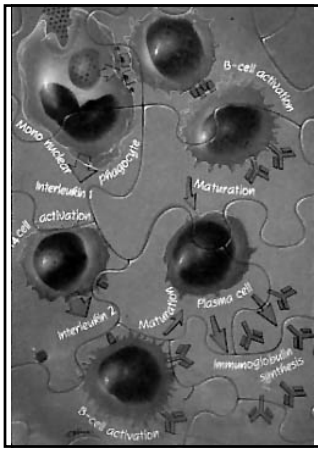


Early Onset Bacterial Infections in the Newborn

- **Incidence: 1- 8/1,000 live births**
- **Mortality: 10 - 25%**
- **Sepsis morbidity: 22% handicaps**
- **Meningitis morbidity: 20 - 50% handicaps**





IMMUNE COMPROMISE

Neonates have immature immune systems with quantitative & qualitative deficiencies in:

- **Phagocytes**
- **Complement**
- **Cytokines**
- **Immunoglobulins**

Pathogenesis of Neonatal Infections

- ***In utero*** **transmission**
- **Acquired during birthing process**
- **Acquired in the 1st month of life**
  - **Nosocomial**
  - **Household**

Perinatal Infections

- **Colonization**
  - **Birth canal**
  - **Ascending infection**
- **Infection**
  - **Direct extension**
  - **Bloodstream invasion**
  - **Swallowed or aspirated amniotic fluid**

Risk Factors

- **Prematurity, low birth weight**
- **Premature ROM (< 34 wks)**
- **Prolonged ROM (> 18 hrs)**
- **Maternal peripartum infection**
- **Septic or traumatic delivery**
- **Fetal/neonatal hypoxia**

Associations

- **Mother's age < 20 years**
- **Multiple gestation**
- **Maternal diabetes**
- **African American race**
- **Male sex**
- **Fetal distress**
- **Traumatic delivery**
- **Indwelling tubes & lines**
- **Surgical procedure**
- **Galactosemia (E. coli)**

Remember:
Only 50-75% have identifiable risk factors or associations

Presentations

- **Early onset (*in utero*):**
  - **Birth through 7 days**
  - **Fulminant presentation (before 12 hrs)**
  - **Pneumonia common, meningitis 10%**
  - **Complications pregnancy & delivery present**
- **Late onset:**
  - **Days 8 through 28 days**
  - **Presents more insidiously**
  - **Meningitis more common (~80%)**
  - **Doubt that obstetric complications contribute**

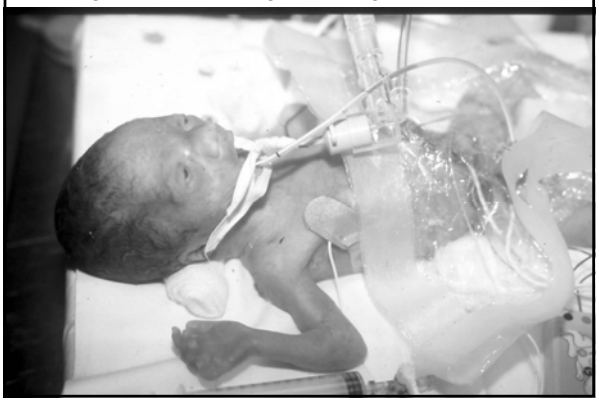
Signs of Sepsis

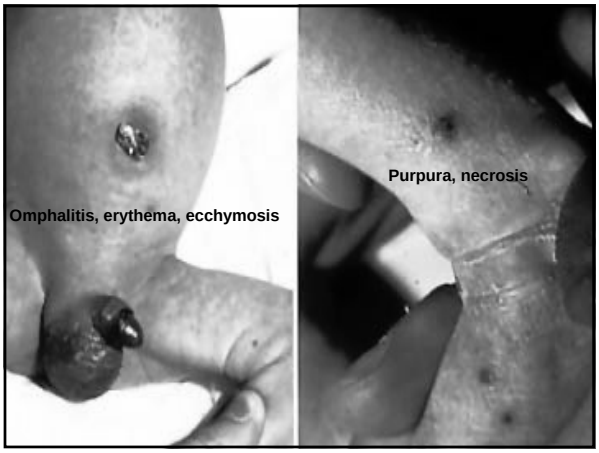
"Anything can be a sign of anything in a neonate" R.A. Polin ~1979

- **Hyperthermia**
- **Hypothermia**
- **Apnea**
- **Cyanosis**
- **Jaundice**
- **Hepatomegaly**
- **Lethargy**
- **Irritability**
- **Anorrhexia**
- **Vomiting**
- **Feeding residuals**
- **Diarrhea**
- **Abdominal distension**
- **"Doesn't look right"**

Subtle Subtle Subtle Subtle Subtle Subtle Subtle Subtle

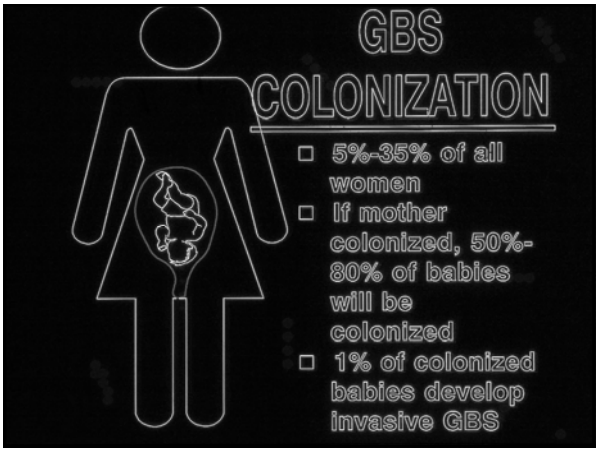
A dirty look: Pale, cyanotic, jaundiced …





Organisms

- Group B Strep (GBS)
- E. Coli
- Other gram negative
  - Klebsiella p.
  - Pseudomonas a.
  - Serratia
- Entarococcus
- Anaerobes
  - Citrobacter
- Viruses
  - Herpes
  - Entaroviruses
- Fungi
  - Candida albicans, or parapsylosis
  - Malesezia furfur
- Viruses
  - Herpes
  - Entaroviruses



Group B Streptococcus

- 50,000 women each year with morbidity
- 8,000-12,000 babies systemically infected
  - 22% initially asymptomatic
  - 70-90% in term infants
  - However, prematures > 4x attack rate
  - Maternal protective IgG crosses after 32 wks
- 1,200-2,000 die annually
- Annual cost > $1,000,000,000

Maternal Morbidity

- Asymptomatic or symptomatic UTI
- Premature rupture of membranes (< 36 wks)
- Prolonged rupture of membranes (> 18 hrs)
- Chorioamnionitis (fever, tenderness)
- Post-partum endometritis (fever, pain, discharge)
- Bacteremia
- Death

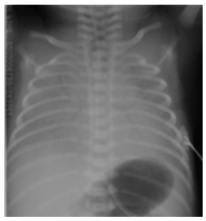
Early Onset GBS Infection

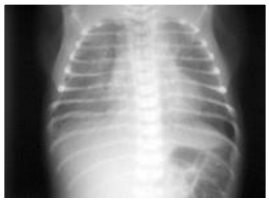
- Occurs at ≤ 7 days of age
- Most are symptomatic within 1-12 hours of birth (thus, were infected *in-utero*)
- Incidence is 1.3-3.7 per 1000 livebirths
- 70%-90% are of term gestation, but prematures have higher attack rates
- Presentation as bacteremia, pneumonia, and meningitis (~10%)

Late Onset GBS Infection

- Occurs beyond 7 days of life
- Mean age of onset is 24 days
- Incidence is 0.5-1.8 per 1000 livebirths
- 70%-85% have meningitis
- 10% mortality, up to 50% neuro sequelae
- 90% due to type III serotype
- 50% acquired at birth from colonized mothers, others acquire it postnatally from mother, community or nosocomially

GBS Pneumonia





The majority of pneumonias associated with GBS will have an initial appearance similar to RDS or TTN

18-22% of babies with Group B Streptococcal bacteremia are asymptomatic

eg, blood cultures obtained for maternal risk factors, or … postmortem!

GBS Disease

- **Bacteremia in only 25%-40%**
  - ***eg*, mother colonized, baby with pneumonia**
- **Pneumonia in 35%-55%**
- **Meningitis in 5%-10%**
- **Current mortality rate is 4%-6%**
- **Higher mortality rate in premature infants**
  - **10% at 34-36 weeks gestation**
  - **30% at < 33 wks)**

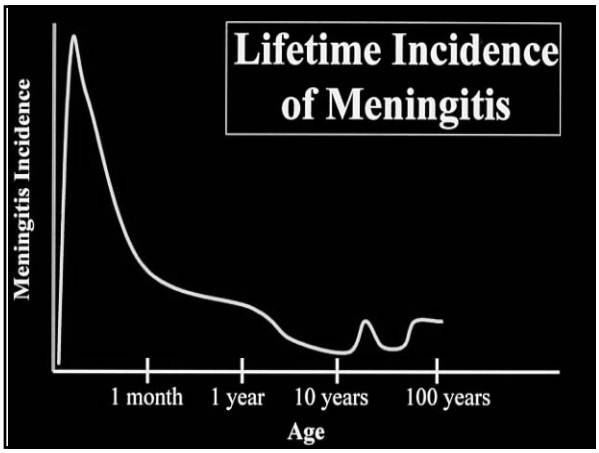
EOS Disease

- Vertical transmission common, some hematogenous-transplacental
- Prematures have 7-fold increase in GBS disease compared to term infants
- EOS GBS disease commonly associated with maternal obstetric complications
- There are 9 total serotypes of GBS: Ia, Ib, II, III, IV, V, VI, VII, VIII
  - EOS typically types 1a, III
  - LOS, meningitis typically type III

LOS Disease

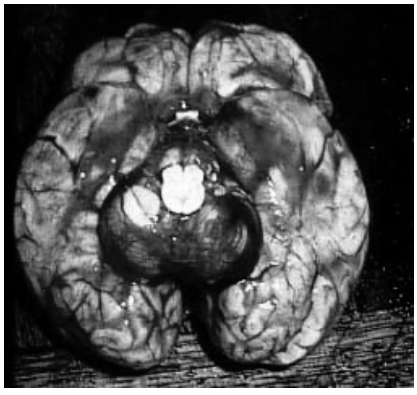
- 3% mortality
- Focal infections are more often seen with LOS disease (eg, osteomyelitis, septic arthritis, cellulitis)
- Term & preterm infants at similar risk
- Horizontal transmission is the major cause of LOS disease

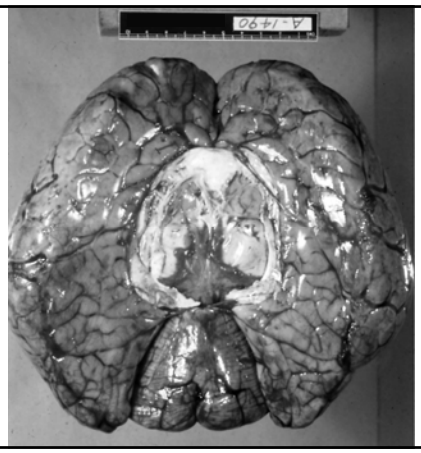
Neonatal Meningitis

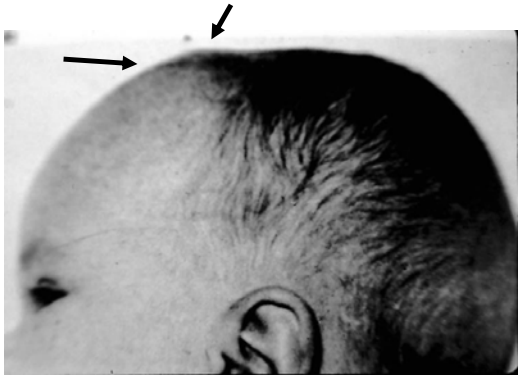


Meningitis Incidence

- **1.3 – 7 per 10,000 live births**
- **5 – 25% culture positive EOS bacteremia complicated by meningitis**
- **15 – 55% culture proven meningitis is blood culture negative**
  - **Meningitis can only be diagnosed by LP with examination & culture of the CSF**







Meningitis Outcomes

- **Mortality ~26%**
- **Of survivors:**
  - **67% normal**
  - **17% major neuro-developmental delays**
  - **16% milder delays**
- **Overall:**
  - **51% die or are abnormal neurologically**

Edwards J PEDIATR 1985;106:717

Meningitis

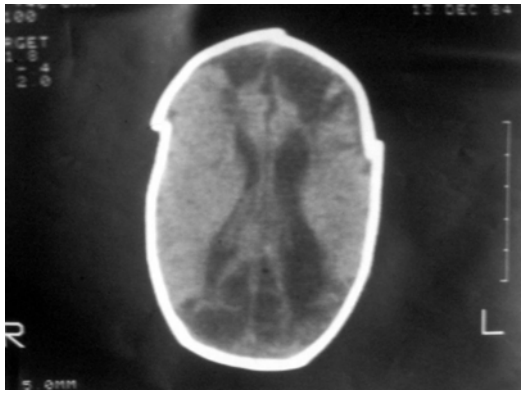
- Decreased meningitis:bacteremia ratio over past 25 years (1:4 → 1:20)
- Mortality rate 3% – 13% in developed countries (↓ from 25% – 30% over last 20 years)
- ↑'d mortality with gram (–) organisms
- Often takes several days for CSF cultures to become sterile, esp. gram (–)'s

Factors Associated with Poor Outcome in Neonatal Meningitis

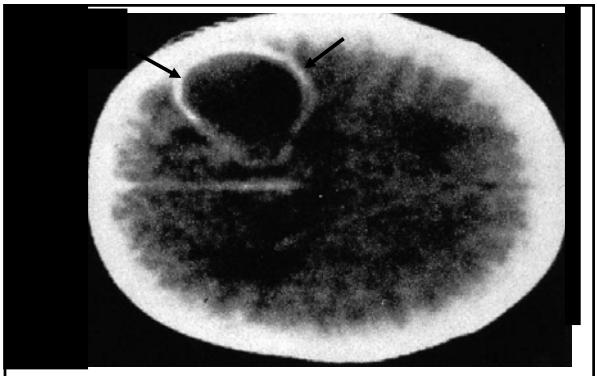
- Very low birth weight
- Coma (& severe lethargy)
- Decreased perfusion
- Need for inotropes to maintain blood pressure
- Seizures (>12 h duration)
- Delay sterilizing CSF
- Peripheral WBC <5,000/mm3
- Absolute neutrophil count (ANC) <1,000/mm3
- Cerebrospinal fluid protein >300 mg/dL
- Abnormal EEG (more than mild)

Meningitis Incidence

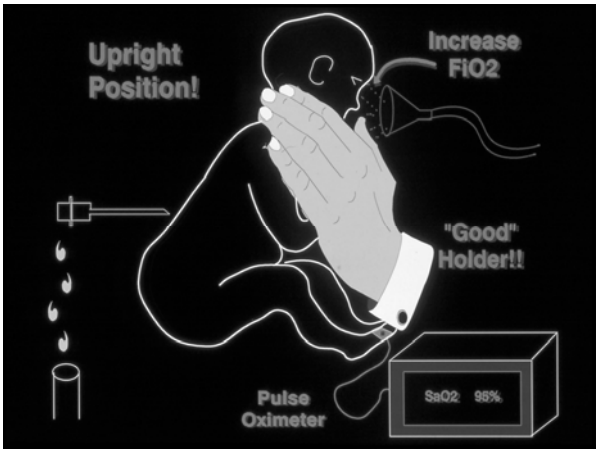
- Likely underestimated
- Many neonates at risk are never evaluated
- Either "too sick" or LP is just never performed, but infant is Rx'd for a "full course" of antibiotics
- Since they are treated with antibiotics for 7-10 days or more, this is enough to sterilize the CSF



Brain atrophy and encephalomalacia following GBS meningitis



<u>Brain Abscess</u>: think *Citrobacter koseri* (*C. diversus*)



Normal CSF Values

- **Cell count:**
  - **0-32 WBC (higher in prematures)**
  - **60% neutrophils (higher in prematures)**
  - **Bloody tap corrections unreliable, repeat LP**
- **Protein**
  - **Mean 90 mg/dL in term infants (20-170)**
  - **Mean 115 mg/dl in preterms (65-150)**
- ***I consider $\geq$ 20 WBC, and protein >80 mg/dL significant in any newborn***

Feigen, McCraken, Klein PEDIATR INFEC DIS J 1992,11:785-814

LP Contraindications

- **Known bleeding disorder**
- **↑ ICP (SDH, EDH, tumor, non-communicating hydrocephalus)**
- **Skin or sub-Q infection at LP site**
- **LS anomalies (spina bifida, meningocele)**
- **Cardiopulmonary instability (must weigh against consequences not treating)**

Consequences Missed or Delayed Diagnosis

- **Antibiotic delay, ↑ morbidity/mortality**
- **Choice, dosage, duration of chemotherapy different**
- **Antibiotics stopped if minimal signs & negative blood culture (partially treated meningitis)**

Neonatal Meningitis Sequelae

- **Mental retardation**
- **Cerebral palsy**
- **Seizures**
- **Blindness**
- **Deafness**
- **Hydrocephalus**
- **Microcephaly**

Nosocomial Infections

- **Infections occurring >48 hours after birth caused by pathogens not maternally-derived**
- **At 25-28 wks gestation ~30% will develop nosocomial infection during hospitalization**
- **At <25 weeks gestation ~46% will develop nosocomial infection during hospitalization**

Nosocomial Infections

- **Common organisms in 1950's and 1960's were *S. aureus* and gram negative rods (*pseudomonas*, *E. coli* and *klebsiella* species)**
- **Since the 1980s, common organisms include coagulase-negative *Staphylococci* and *Candida* species (*albicans and parapsilosis*)**
- **New worries: methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant *enterococci* (VRE), and other multiply resistant gram negative organisms**

Nosocomial Infections

- **Increase cost of neonatal care**
- **Prolong hospitalization**
- **Responsible for 50% of neonatal deaths beyond two weeks of age**
- **High mortality rates with infections due to *Pseudomonas* and *Candida* species**
- **Candida species frequently cause meningitis**

Coagulase Negative Staphylococci (CoNS)

- **Most common cause of neonatal nosocomial infections (>40%)**
- **Besides bacteremia, CoNS can cause meningitis, necrotizing enterocolitis, shunt infections, *and* endocarditis**
- **CoNS sepsis is generally more indolent than other organisms, but is occasionally fulminant and fatal**

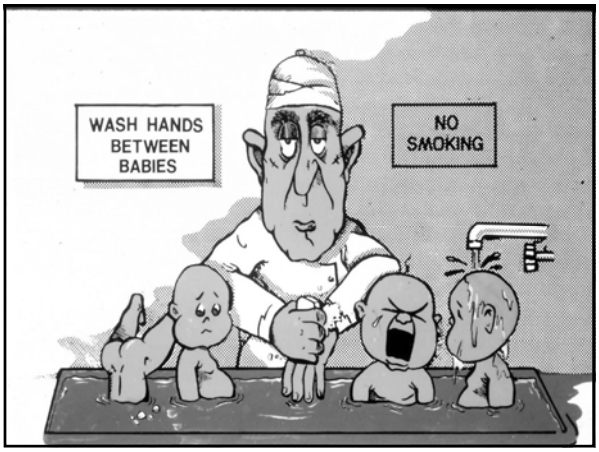
Coagulase Negative Staphylococci (CoNS)

- **Increased incidence of CoNS since 1970's and 1980's mainly due to improved survival, increased use of catheters, and prolonged hospitalization**
- **Risk factors for CoNS:**
  - **Use of central venous catheters**
  - **Intravenous lipids (M. furfur)**
  - **Prolonged use of TPN**
  - **Mechanical ventilation**
  - **Increased severity of illness**

Prevention of Nosocomial Infection

- **Good handwashing (before *&* after contacts)**
- **De-germing (alcohol-based hand rub with emollient)**
- **Sterilize resuscitation bags and masks**
- **Minimize use of central venous catheters**
- **Minimize time on mechanical ventilation**
- **Use antibiotic-coated or silver sulfadazine-impregnated catheters**

THESE ARE PROVEN EFFECTIVE MEASURES!



Handwashing in the NICU

Nurses, physicians, visitors …

- **2 New York City Hospitals assessed**
- **Each neonate or his/her environment was touched on average 78x per 12 hour shift**
- **Only 23% of health care professionals/visitors preceded touching with either washed or newly-gloved hands**

Larson E, Columbia University, 2003.

Prevention of Nosocomial Infection

- Prevent preterm births
- Eliminate overcrowding and understaffing
- Careful preparation and storage of infant formulas and breast milk
- Decrease the number of heel sticks and venipunctures
- Use single dose medications
- Avoid drugs associated with increased infections (steroids, histamine$_2$ blockers)

Prevention of Nosocomial Infection

- Antibiotic prophylaxis, *eg* add vancomycin or fluconazole to IV & TPN solutions
- Immunoprophylaxis:
  - routine IV-Ig infusion
  - High-titer IV-Ig (*vs* S. epidermidis, S. aureus)
- Granulocyte colony-stimulating factor (G-CSF)
- Granulocyte-macrophage colony-stimulating factor (Gm-CSF)

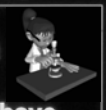
THESE HAVE NOT
PROVEN
EFFECTIVE

Diagnosis

CBC

- Low total WBC (<5,000)
- High total WBC (>25-30,000)
- Low absolute neutrophil count (<1500)
- High Immature:Total ("I:T") ratio (>0.20)
- Thrombocytopenia (<100,000)

HEMATOLOGIC PREDICTORS OF NEONATAL SEPSIS



- Many septic infants have a normal initial CBC
- Many non-infected infants have an abnormal initial CBC
- Low positive predictive values (on the order of 10%)
- Best use is their high negative predictive value (if studies are normal, rarely infected)

OTHER SUPPORTIVE SCREENING LABORATORY TESTS

- C-reactive protein
- Erythrocyte sedimentation rate
- Haptoglobin
- Fibronectin
- Orosomucoid

*None are readily available in most settings

Other Immunological Markers of Infection

- Cytokine levels:
  - IL-1β
  - IL-6
  - TNFα
  - IL-1 receptor antagonist
  - Il-8
- Fibronectin levels
- Neutrophil elastase inhibitor levels
- Neutrophil CD11b levels

Other Immunological Markers of Infection

- **Polymerase chain reaction (PCR)**
- **Pro-calcitonin level (may be the best)**
- **TNF receptor p55 and p75 levels**
- **Soluble intracellular adhesion molecule levels**

Other Complementary Tests to the Diagnosis of Infection

- **Heart rate analysis**
- **Central & peripheral temperatures**
- **Urinary nitric oxide**
- **Sepsis scores**

CHEST X-RAY

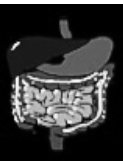
- EARLY-ONSET SEPSIS
  - PNEUMONIA VERY COMMON
  - MAY NOT BE SYMPTOMATIC BUT USUALLY ARE
  - ? REQUIRED IN ALL EVALUATIONS?
- LATE-ONSET SEPSIS
  - PNEUMONIA STILL COMMON
  - MAY NOT BE SYMPTOMATIC, THOUGH LESS LIKELY
  - ? REQUIRED IN ALL EVALUATIONS ?

URINE

- Yield is low in early onset sepsis
- Blood usually positive for same bug
- Don't withhold therapy for culture
- Suprapubic & cather specimens only

TRACHEAL ASPIRATE CULTURES

- Do not predict which infants will become septic (either early-onset or late onset sepsis)
- Surveillance cultures of ventilated infants are of virtually no value



Gastric/Ear Smears & Cultures

- Specimens examined for PMN's and bacteria
- Presence indicates exposure, not infection
- Of limited value in identifying infants at risk for sepsis

Rx Rx

- A penicillin and an aminoglycoside
- Supportive therapy (for blood pressure, ventilation, etc)

Rx Rx

Choosing Chemotherapy: *'KISS'*

"Keep it simple stupid!"

- **1st line emperic therapy, < 2 weeks old**
  - **Ampicillin & gentamicin**
- **1st line emperic therapy, > 2 weeks old**
  - **Vancomycin & cefotaxime**
- **Add ambisome if low platelets & indolent capillary leak**
- **Add acyclovir if history suggests – or fever, rapid deterioration, seizures, liver &/or platelet involvement**

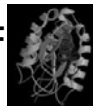
Neonatal Anti-microbial Dogma

- **"Anything can be a sign of anything in the neonate" *Richard A. Polin***
- **Gram negative bacillus infections are usually 2-drug bugs, so are Listeria and GBS**
- **The correct course of chemotherapy for bacterial infection in culture-negative neonatal sepsis is 2, 3, 5, 7, 10, 12, 14, or 21 days (ask anyone to decide)**
- **When starting antibiotics determine criteria to stop them**
- **Better is less – <u>wait</u> for culture & sensitivity results to broaden or focus treatment**

Agents to Reduce Inflammation

- **Corticosteroids**
- **Anti-cytokine antibodies or cytokine inhibitors**
- **Anti-endothelium leukocyte adhesion agents**
- **<u>None</u> of these have been demonstrated to be effective in managing neonatal bacteremia or meningitis**

Immunotherapy

- **Intravenous gammaglobulin (IVIG)**
- **Granulocyte transfusions**
- **Hematopoietic growth factors:**
  - **G-CSF** 
  - **GM-CSF** 

<u>None</u> of these have been demonstrated to be effective in managing neonatal bacteremia or meningitis

REFERENCE FOR AGENTS, DOSAGES BY AGE, INTERVALS, LEVELS:

ROSS neofax 2007
20th Edition
TE Young & B Mangum
Acorn Publishing, Inc.

www.neofax.com

Chemoprophylaxis

Indications for IAP to prevent GBS

Vaginal and rectal GBS screening cultures at 35 to 37 weeks gestation for <u>all</u> pregnant women unless patient had GBS bacteriuria during the current pregnancy or previously had an infant with invasive GBS disease

Optimize Maternal Cultures

- **Obtain cultures from both the vaginal introitus and the ano-rectum**
- **Transport and process in a selective broth medium (contains antibiotics to suppress other bacterium)**
- **If non-selective mediums are used, 50% of cases are missed**

Intrapartum Propylaxis Indicated

•Previous delivery of an infant with invasive GBS disease

•GBS bacteriuria during current pregnancy

•Positive GBS screening culture during current pregnancy (unless a planned cesarean delivery is performed in the absence of labor or amniotic membrane rupture)

*MMWR 2002;51(RR-11):1-21

Intrapartum Propylaxis Indicated

•Unknown GBS status (culture not done or incomplete, or results unknown) *and* any of the following:

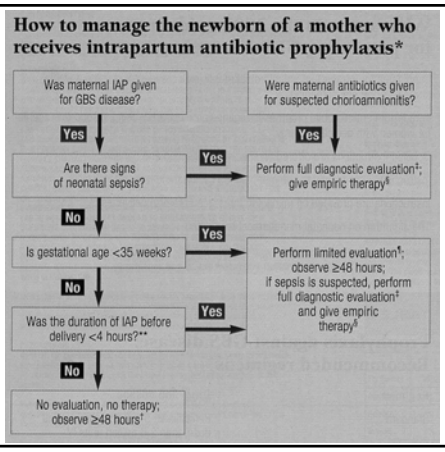
- **Delivery at < 37 weeks G.A.**
- **Amniotic membrane rupture ≥ 18 hours**
- **Intrapartum maternal temperature ≥ 100.4º F (≥38º C)**

*MMWR 2002;51(RR-11):1-21

Intrapartum Propylaxis *Not* Indicated

- **Positive GBS screening culture in previous pregnancy (unless current culture also positive)**
- **Planned C-section with absence of labor or membrane rupture (regardless of maternal GBS culture)**
- **Negative vaginal/rectal GBS screening culture in late gestation during current pregnancy, regardless of intrapartum risk factors**

*MMWR 2002;51(RR-11):1-21



Management of Newborn whose Mother had IAP

- Full evaluation includes CBC/diff, blood culture, and CXR if respiratory abnormalities. If signs of sepsis are present, a lumbar puncture, if feasible, should be performed
- Duration of antibiotics varies with culture results and infant's clinical course. If lab studies and clinical course do not indicate sepsis, stop antibiotics at 48 hours

*MMWR 2002;51(RR-11):1-21

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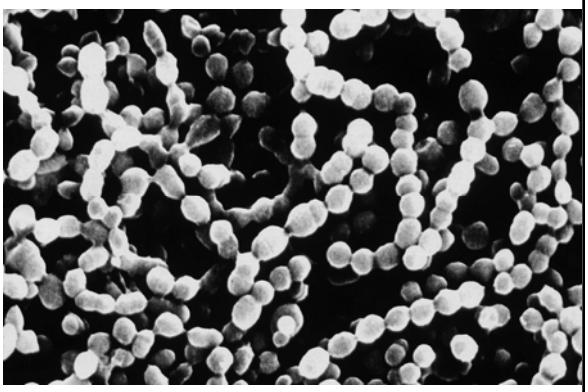
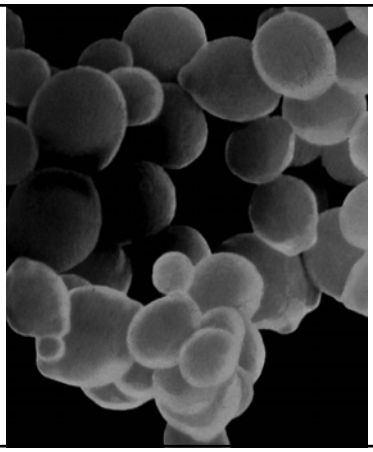




The End

Questions

- Should we sedate babies before the procedure?
- Should we use local anesthesia?
- Should we aspirate the stomach prior to the LP?
- What is the best position to put the babies in?
- Which babies should we defer the LP because of "instability"… should we at least attempt it in all neonates and stop when necessary?
- Should we continue to perform antigen testing?

Considerations

Statistically: Low yield; therefore, do selectively

Clinically: Changes management and prognosis, do in all

Legally: High incidence of meningitis during first week of life

Low risk procedure

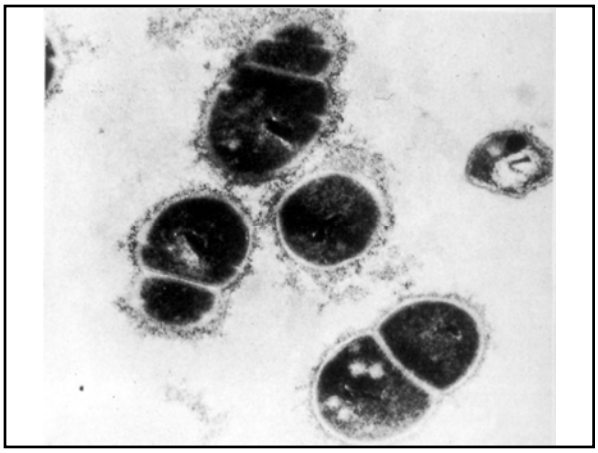
The only way of confirming meningitis is by evaluating the CSF

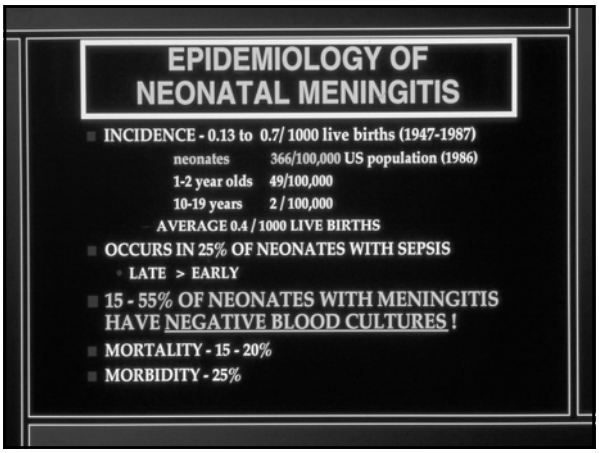
Potential Extent of Problem

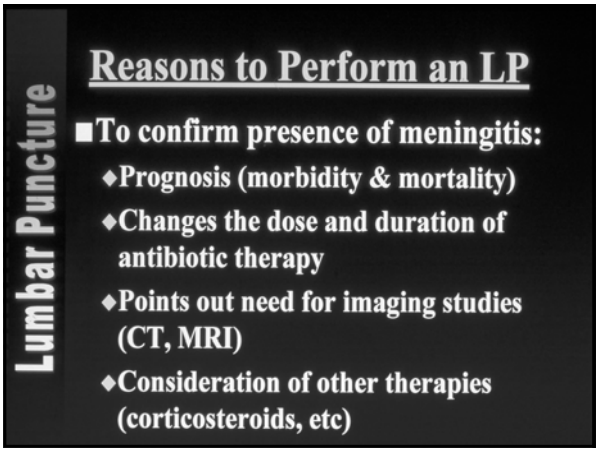
Workup and Management

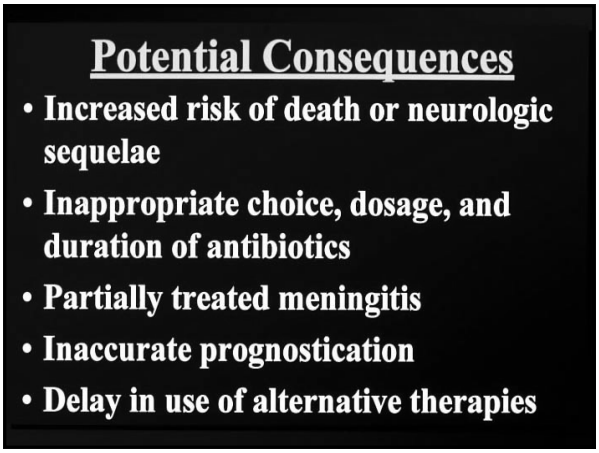
- Suspected chorioamnionitis 3%
- Maternal fever 10%
- + GBS maternal culture 5%-35%
- Premature 8%
- Maternal bacteriuria with GBS 1%
- PROM 7%
- Prior sibling with GBS < 1%

Total = 20% - 50% of all deliveries




EPIDEMIOLOGY OF
NEONATAL MENINGITIS
INCIDENCE - 0.13 to 0.7/ 1000 live births (1947-1987)
neonates 366/100,000 US population (1986)
1-2 year olds 49/100,000
10-19 years 2 / 100,000
AVERAGE 0.4 / 1000 LIVE BIRTHS
OCCURS IN 25% OF NEONATES WITH SEPSIS
LATE > EARLY
15 - 55% OF NEONATES WITH MENINGITIS HAVE NEGATIVE BLOOD CULTURES !
MORTALITY - 15 - 20%
MORBIDITY - 25%


Lumbar Puncture
Reasons to Perform an LP
To confirm presence of meningitis:
Prognosis (morbidity & mortality)
Changes the dose and duration of antibiotic therapy
Points out need for imaging studies (CT, MRI)
Consideration of other therapies (corticosteroids, etc)


Potential Consequences
• Increased risk of death or neurologic sequelae
• Inappropriate choice, dosage, and duration of antibiotics
• Partially treated meningitis
• Inaccurate prognostication
• Delay in use of alternative therapies

Conundrum

The sickest infant, the one you would most likely defer performing an LP on because of instability, has the greatest likelihood of having meningitis

Indications for intrapartum antibiotic prophylaxis to prevent GBS disease

Vaginal and rectal GBS screening cultures at 35 to 37 weeks' gestation for *all* pregnant women (unless patient had GBS bacteriuria during the current pregnancy or previously had an infant with invasive GBS disease)

Intrapartum prophylaxis indicated

- ☐ Previous delivery of an infant with invasive GBS disease
- ☐ GBS bacteriuria during current pregnancy
- ☐ Positive GBS screening culture during current pregnancy (unless a planned cesarean delivery is performed in the absence of labor or amniotic membrane rupture)
- ☐ Unknown GBS status (culture not done or incomplete, or results unknown) and any of the following:
  - Delivery at <37 weeks' gestation*
  - Amniotic membrane rupture ≥18 hours
  - Intrapartum temperature ≥100.4° F (≥38.0° C)**

Intrapartum prophylaxis not indicated

- ☐ Positive GBS screening culture in previous pregnancy (unless a culture was also positive during the current pregnancy)
- ☐ Planned cesarean delivery performed in the absence of labor or membrane rupture (regardless of maternal GBS culture status)
- ☐ Negative vaginal and rectal GBS screening culture in late gestation during current pregnancy, regardless of intrapartum risk factors

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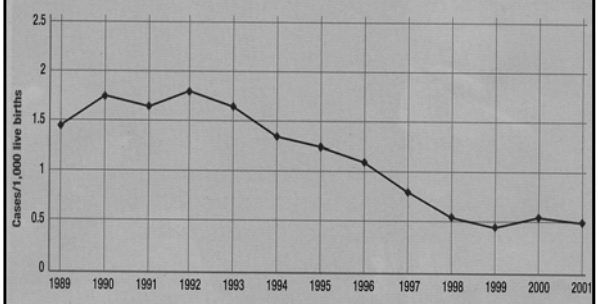
FIGURE 1

Tracking a decline in early-onset invasive GBS disease



Incidence fell dramatically through the 1990s thanks to an increase in the use of intrapartum antibiotic prophylaxis.

Adapted from *MMWR Morb Mortal Wkly Rep* 2002;51(No. RR-11)[1]