# Neonatal Infections

## Block 10

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# Introduction

- Infection is a leading cause of neonatal mortality and morbidity
- The smaller and more preterm the baby: the higher the risk of infection and its consequences
- Early detection and prompt management is vital in the prevention of adverse consequences

# Definition

- Neonatal sepsis: infection occurring within the neonatal period
  - Term baby: 1st 28 days of life
  - Preterm baby: up to 4 weeks beyond the expected date of delivery
- Broadly classified into two groups
  - Early-onset sepsis
  - Late-onset sepsis

# Early-onset Sepsis EOS [1]

- Clinical challenge
  - Multiple routes of transmission
  - Change in causative agents
  - Potential antibiotic resistance
- Definition
  - Various definitions, subtle differences
  - EOS refers to an infection of the bloodstream or meninges proven by culture
  - Usually acquired vertically from the mother and manifests shortly after birth: with 48-72 hours

## Early-onset Sepsis EOS 2

- Presentation
  - Subtle early signs or fulminating septicaemia
  - Most common focal infection: pneumonia
- Main routes of transmission
  - Trans-placental
  - Ascending vaginal route

## Early-onset Sepsis EOS 3

- Causative agents
  - Predominantly Group B streptococcus (GBS)
  - Gram negative isolates
    - *Escherichia Coli*
  - Other
    - Streptococci
    - *Staphylococcus aureus*

## Causative organisms: United States

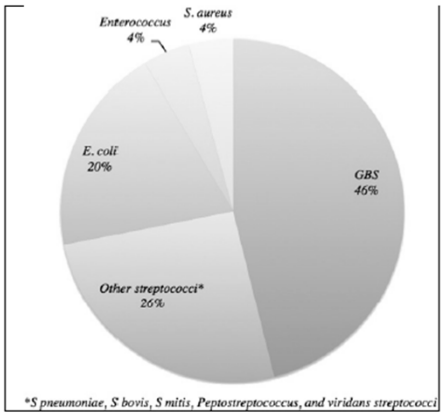


Figure 1. Early onset sepsis in the United States.

## Causative organisms: Very low birth weight infants in united states

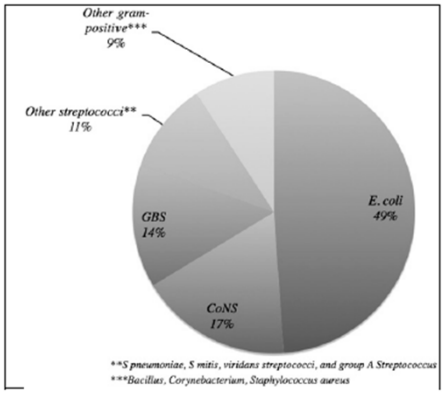


Figure 2. Early onset sepsis among very low birth weight infants in the United States.

## Causative organisms: Developing nations

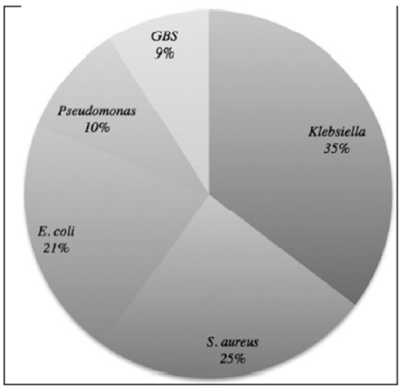


Figure 3. Early onset sepsis in developing nations.

## Late-onset Sepsis LOS [1]

- Definition
  - Varying definitions
  - Most frequently defined as infection occurring at more than 48 – 72 hours after birth
- Main routes of transmission
  - Nosocomial
  - Horizontal transmission

# Late-onset Sepsis LOS [2]

- Risk factors

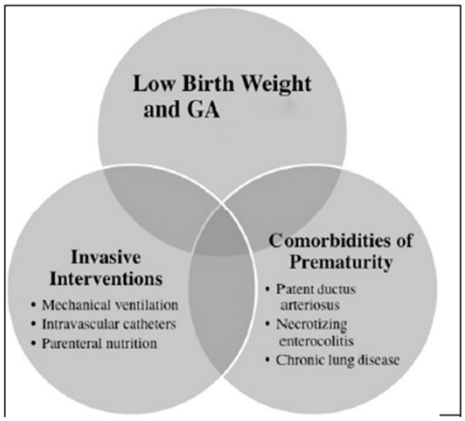


Figure. Factors that confer a greater risk for LOS in the neonate.

# Late-onset Sepsis LOS [3]

- Risk factors for nosocomial infection
  - Intensive care admission
  - Not receiving enteral feeds ( esp gut-surgery)
  - Not receiving maternal breastmilk
  - Indwelling catherization
  - Total parenteral nutrition

## Late-onset Sepsis LOS [4]

- Antibiotic-related risk factors for LOS:
  - Prolonged initial empirical antibiotic treatment
    - (> 5days) is associated with increased rates of necrotising enterocolitis and death in ELBW infants
  - Prolonged use
    - Increased antibiotic resistance among normal commensal organisms
    - Emergence of other pathogens

## Late-onset Sepsis LOS [5]

- Risk factors for yeast infections
  - H-2 receptor antogonists
  - Abdominal surgery
  - Peritoneal dialysis
  - Exposure to broad-spectrum antibiotics especially 3rd generation cephalosporins
  - Antenatal antibiotics

## Late-onset Sepsis LOS [4]

- Causative agents
  - Coagulase-negative staphylococci (CoNS)
  - *S.aureus*
  - *E. coli*
  - *Enterococcus*
  - Enterobacteriaceae
  - Yeasts
    - *Candida albicans,*
    - *C. parapsilosis*

## Clinical Presentation [1]

- Early stages of infection: clinical signs may be very subtle
  - Poor feeding
  - Excessive sleepiness
- Most common presenting signs of infection
  - Tachypnoea
  - Apnoea
  - Respiratory distress

## Clinical Presentation 2

- Ventilated baby
  - Increased ventilator requirements
- Alternative presentation
  - Respiratory failure
  - Cyanosis
  - Shock
- EOS may be indistinguishable from hypoxic ischaemic encephalopathy at delivery

## Clinical Presentation 3

- Progression from mild symptoms to death can occur in < 24 hours especially with certain organisms: GBS, *E.coli*
- GBS
  - RDS and GBS radiologically indistinct
  - Can be complicated by development of PPHN, hypotension, metabolic acidaemia, tachycardia, poor peripheral perfusion

## Clinical Presentation [4]

- Temperature
  - Temperatures < 36 $^{o}$ C or > 37.8 $^{o}$ C sustained for > 1 hour: infection until proven otherwise
  - Unremitting fever: most likely viral origin
- Common features of generalised sepsis and NEC
  - Milk intolerance
  - Abdominal distension

## Physical Examination [1]

- Assessment should include
  - Posture and tone
  - Colour
  - Level of activity
  - Capillary refill time: marker of perfusion
  - Skin lesions: erythema, petechiae, mottling
  - Signs of respiratory distress: tachypnoea, grunting, moaning, abnormal breath sounds
  - Bradycardia vs tachycardia

# Physical Examination 2

- Assessment
  - Bowel sounds absent in NEC & functional ileus
  - Late features of meningitis
    - High-pitched cry
    - Abnormal movements
    - Back-arching
    - Tense fontanelle
  - LOS: limbs and joints: osteomyelitis, septic arthritis

# Investigations 1

- A baby with features attributable to infection
  - Prompt evaluation, investigation and treatment
  - Deterioration can be rapid and unremitting

# Investigations 2

- Special investigations should include
  - Blood culture
    - Aseptic technique
    - The greater the volume, the greater the yield
    - Most significant cultures are positive by 48 hours
  - Surface swabs, tracheal secretions, endotracheal tube-tip culture and gastric aspirates
    - Limited value regarding likely infecting pathogen
    - Informative about colonization

# Investigations 3

- Special investigations should include
  - Urine
    - Supra-pubic/ catheter specimen
    - $\geq 10^8$ organisms/litre of urine
  - Lumbar puncture
    - Thrombocytopaenia is a relative contra-indication
  - Radiology
    - Chest or abdominal x-ray

# Investigations 4

- Haematological investigations
  - Full blood count
    - Neutrophil count
      - Neutropenia: high mortality
      - Band cells: immature circulating neutrophils
      - Toxic granulation
    - Lymphocyte count
      - Lymphocytosis: viral infection
      - Persistent lymphopenia: immunodeficiency

# Investigations 5

- Haematological investigations
  - Full blood count
    - Platelet count
      - Thrombocytopenia: common feature of generalized infection and NEC, HIE, viral infections ( rubella, CMV, herpes, enterovirus)
      - Thrombocytosis: chronic inflammation

# Investigations 6

- Haematological investigations
  - Liver function tests
    - Viral & bacterial infections: abnormal liver tests, jaundice, bleeding tendencies

# Investigations 7

- Haematological investigations
  - Acute phase reactants
    - CRP
      - Most commonly available acute phase reactant
      - Levels rise in response to IL-6
      - Babies with positive blood cultures may have negligible CRP results at birth but CRP rises 12 hours later
      - Serial measurements: useful to monitor progression of infection, guide treatment

# Investigations 8

- Haematological investigations
  - Acute phase reactants
    - Procalcitonin
      - More sensitive than CRP to differentiate between neonatal infection and inflammation
      - Differentiate between bacterial and viral infections

# Investigations 9

- Haematological investigations
  - Polymerase chain reaction (PCR)
    - Measures highly conserved DNA sequences from Gram positive and Gram negative organisms and many viruses
    - Potential to provide more rapid diagnosis of bacteraemia and viraemia

## Investigations [10]

- Further special investigations
  - If fungal sepsis is suspected or diagnosed
    - Abdominal and renal ultrasound
    - Cranial ultrasound
    - Fundoscopy
    - Echocardiogram

## Treatment of neonatal sepsis [1]

- Prompt treatment with appropriate antibiotics
- Narrow-spectrum antibiotics should be used wherever possible
- Broad-spectrum antibiotics held in reserve
- Colonization of babies without clinical signs of infection does not warrant antibiotics
- There are no definitive randomized trials regarding best antibiotic regimens for the newborn
- Each antibiotic has benefits and side-effects

# Treatment of neonatal sepsis [2]

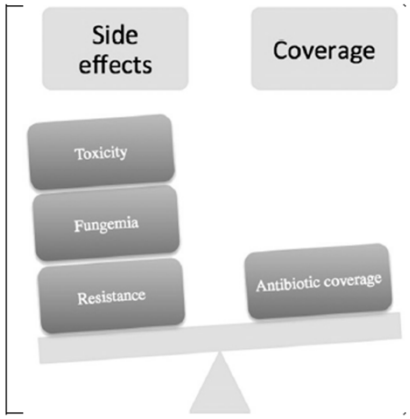


Figure 4. Risk benefit uneven.

# Treatment of neonatal sepsis [3]

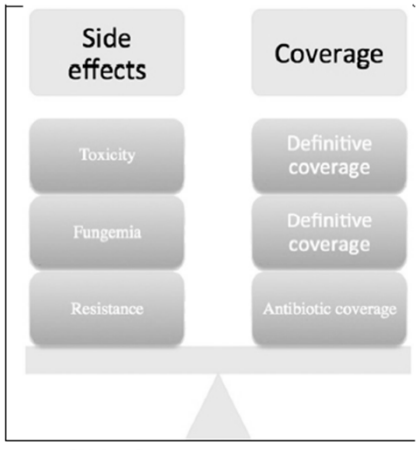


Figure 5. Risk benefit even.

## Treatment of neonatal sepsis 4

- Antibiotic choices for EOS
  - Benzyl penicillin with aminoglycoside
    - Excellent coverage for EOS pathogens
    - Relatively narrow spectrum
  - Cephalosporins
    - Broad spectrum of activity
    - Greater potential harm
  - If *S.aureus* is suspected: Flucloxacillin
  - If *L.monocytogenes* is suspected
    - Amoxicillin substituted for benzyl penicillin

## Treatment of neonatal sepsis 5

- Antibiotic choices for LOS
  - Majority of causes other than Coagulase-negative staphylococci (CoNS) : narrow-spectrum combination
  - CoNS
    - Vancomycin & teicoplanin
    - Risk: of vancomycin-resistant enterococcal infections and resistant gram-negative infections
    - Empiric use should only target those babies with highest risk of complicated CoNS

# Treatment of neonatal sepsis [6]

- Antibiotic choices for LOS
  - *S. aureus:* Flucloxacillin
  - Cephalosporin (alone/combination) inadequate cover for a number of Enterobacteriaceae
  - If inadequate clinical improvement or deterioration: repeat blood cultures and change antibiotic therapy

# Treatment of neonatal sepsis [7]

- Antibiotic choices for LOS
  - Vancomycin: bacteriocidal activity is related to its trough concentration; vital that concentration above minimal inhibitory concentration (MIC) at all times
  - Antibiotic therapy should be stopped after 36-48hours if cultures are negative and baby is asymptomatic
  - If culture is positive: adapt treatment, narrowest spectrum possible

## Treatment of neonatal sepsis 8

- Disadvantages of aminoglycosides
  - Excellent narrow-spectrum coverage
  - Narrow therapeutic window: measurement of levels
  - Ototoxicity and sensori-neural hearing loss

## Treatment of neonatal sepsis 9

- Monitoring response to therapy
  - Antibiotic therapy alone may not clear infection
  - Persistence of positive blood cultures: furthur investigations required
  - Blood cultures remain positive
    - Inadequate antibiotic levels or regimens
    - Resistent organisms
    - Colonization of indwelling long lines, umbilical artery or venous lines
    - Focal infections: necrosis of gut, abscess formation, osteomyelitis or endocarditis

# Treatment of neonatal sepsis [10]

- Length of treatment
  - Whilst antibiotic therapy must be commenced promptly for suspected infection, they should be stopped as soon as sepsis has been excluded
  - Little published evidence to inform of optimal length of course of antibiotics
  - Prolonged duration of initial empirical antibiotic treatment (> 5 days): associated with increased rates of NEC and death in ELBW

# Treatment of neonatal sepsis [11]

- Length of treatment
  - If antibiotics are started due to possibility of infection but baby is asymptomatic and all cultures are negative at 36-48 hours: stop antibiotics
  - If blood cultures are negative but clinically sepsis is evident: antibiotics for 5 days
  - If blood cultures are positive but CSF cultures are negative: treatment for minimum of 10 days
  - *S. aureus:* minimum treatment duration of 14 days
  - Positive CSF cultures: treatment duration for at least 21 days

# Treatment of neonatal sepsis 12

- Potential hazards of peri-partum antibiotic usage
  - Reduced incidence of specific invasive infections especially GBS
  - But there are a number of potential adverse consequences
    - Altered natural microflora of the gut
    - Resistance among normal commensal organisms
    - Emergence of other pathogens
  - Linked to increased incidence of allergic and auto-immune disease in young children

# Treatment of neonatal sepsis 13

- Feeding and infection prevention
  - The earlier enteral feeds are commenced, the sooner a baby is receiving full enteral feeds, the less likely the baby is to develop LOS
  - Breatmilk has been shown to protect babies from LOS and to protect against NEC
  - Trophic feeds: facilitate the naive gut becoming colonized with normal bacteria ( lactobaciilli and bifdobacteria)
    - Critical for the development of the immune system
    - Development of mucosal barrier function, gut motility and digestive functions

# Treatment of neonatal sepsis [14]

- Feeding and infection prevention
  - The gut bacteria in preterm babies is dominated by CoNS – the most common organism causing LOS
  - Bacteria from gut ''translocate'' across immature gut mucosa: poor barier to infection in a non-fed, neonate
  - Translocating bacteria may colonise indwelling devices causing systemic infection

# Congenital Infections

- TORCHES
  - T Toxoplasmosis
  - O Other viruses
  - R Rubella
  - C Cytomegalovirus
  - He Herpes virus
  - S Syphilis

Thank You

# References


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2. Falciglia G, Hageman JR, Schreiber M, Alexander K. Antibiotic Therapy and Early Onset Sepsis. *Neoreviews* 2012;13;e86
3. Chu A, Hageman JR, Schreiber M, Alexander K. Antimicrobial Therapy and Late Onset Sepsis. *Neoreviews* 2012; 13; e94