Sepsis

NICU

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Early Onset Sepsis vs. Late Onset Sepsis

Early Onset Sepsis

Per WHO:

- Onset of symptoms before 72 hours of age (first seven days?)
- Causes ~8% of neonatal deaths

EOS

Epidemiology

- Decrease in incidence since initiation of national guidelines for intrapartum antibiotic prophylaxis in 1996
- Current EOS incidence: 0.8-1.1/1000 live births
- Preterm infants are at increased risk for EOS compared to term infants
    - The more preterm, the higher the incidence

EOS

Microbiology

- Pathogenesis of EOS is most commonly that of ascending colonization of the uterine compartment with maternal GI/GU organisms during L&D
    - Blood borne transmission across placenta can also occur, less commonly
        - Listeria monocytogenes

EOS

Microbiology

- Microbiology differs between term and preterm infants
- TERM:
  - MOST COMMON: Group B Streptococcus (GBS)
    - Incidence has decreased with antenatal screening for GBS and IAP
  - Escherichia coli
- PRETERM:
  - MOST COMMON: E. coli (~50%)
- Other common pathogens (account for ~1/3 of cases):
  - Gram positive: Staphylococcus aureus, Enterococcus, Streptococcus, Listeria (rarely)
  - Gram negative: Haemophilus, Klebsiella
- Fungal: Candida (mainly in very premature infants)

EOS

Risk Factors

- Maternal
  - Factors that facilitate pathogenesis
    - Duration of ROM, PROM, GBS colonization, prior birth of infant with GBS infection, ingestion of listeria contaminated foods, mode of delivery
  - Factors associated with evolving infection (provides a sign infection may be present)
    - Intrapartum fever, confirmed intraamniotic infection, PTL, maternal tachycardia
- Neonatal
  - Factors that facilitate pathogenesis
    - Prematurity, LBW, male sex
  - Factors associated with evolving infection
    - Clinical illness, meconium stained amniotic fluid, fetal tachycardia

EOS

Risk Factors

- THREE STRONGEST PREDICTORS:
  - Gestational age, intraamniotic infection, neonatal clinical illness
- Chorioamnionitis is strongly associated with risk of EOS

EOS Risk Assessment

EOS Calculator

RESEARCH

Probability of Neonatal Early-Onset Sepsis Based on Maternal Risk Factors and the Infant's Clinical Presentation

Predictor	Scenario
Incidence of Early-Onset Sepsis	0.3/1000 live births (KPNC incidence)
Gestational age	weeks days
Highest maternal antepartum temperature	Fahrenheit
ROM (hours)	
Maternal GBS status	Negative Positive Unknown
Type of intrapartum antibiotics	Broad spectrum antibiotics ≥ 4 hrs prior to birth Broad spectrum antibiotics 2-3.9 hrs prior to birth GBS specific antibiotics ≥ 2 hrs prior to birth No antibiotics or any antibiotics < 2 hrs prior to birth

	Risk per 1000/births	Clinical Recommendation
EOS Risk @ Birth		

Clinical Exam	Risk per 1000/births	Clinical Recommendation
Well Appearing		
Equivocal		
Clinical Illness		

Calculate Clear

- For infants >/= 35 weeks

Classification of Infant's Clinical Presentation (Hide)

Clinical Exam	Description
Clinical Illness	1. Persistent need for NCPAP / HFNC / mechanical ventilation (outside of the delivery room) 2. Hemodynamic instability requiring vasoactive drugs 3. Neonatal encephalopathy /Perinatal depression • Seizure • Apgar Score @ 5 minutes < 5 4. Need for supplemental O_2 ≥ 2 hours to maintain oxygen saturations > 90% (outside of the delivery room)
Equivocal	1. Persistent physiologic abnormality ≥ 4 hrs • Tachycardia (HR ≥ 160) • Tachypnea (RR ≥ 60) • Temperature instability (≥ 100.4˚F or < 97.5˚F) • Respiratory distress (grunting, flaring, or retracting) not requiring supplemental O_2 2. Two or more physiologic abnormalities lasting for ≥ 2 hrs • Tachycardia (HR ≥ 160) • Tachypnea (RR ≥ 60) • Temperature instability (≥ 100.4˚F or < 97.5˚F) • Respiratory distress (grunting, flaring, or retracting) not requiring supplemental O_2 Note: abnormality can be intermittent
Well Appearing	No persistent physiologic abnormalities

EOS Risk Assessment

Preterm Infants

- Preterm infants have inherent physiologic instability making it difficult to distinguish when such instability is related to prematurity or due to infection
- Incidence of chorioamnionitis increases with decreasing GA
    - Infection is a common cause of PROM/PTL
- Death attributable to EOS is inversely related to GA
    - Gram negative/fungal with high mortality association
- Low risk delivery characteristics

EOS

PREVENTION

- Risk of overuse of antibiotics
  - NEC, antibiotic resistance, subsequent late infection, death
- Only intervention proven to reduce incidence of EOS is targeted IAP

EOS

Clinical Features

- Things to consider:
  - TERM:
    - Concern for maternal infection? GBS status? Clinical illness?
  - PRETERM:
    - Why was the infant delivered? Maternal reasons? Was their PTL/PROM?

EOS

Diagnosis

- Gold standard: blood culture
- What we send:
  - CBC ~6 hours of life
  - Blood culture x1 (1ml blood/bottle)
    - Some centers send 2 to distinguish contaminant from true infection
  - Some centers send CRP, procalcitonin (biomarkers of inflammation)
- CSF is obtained if blood culture positive and concern for meningitis

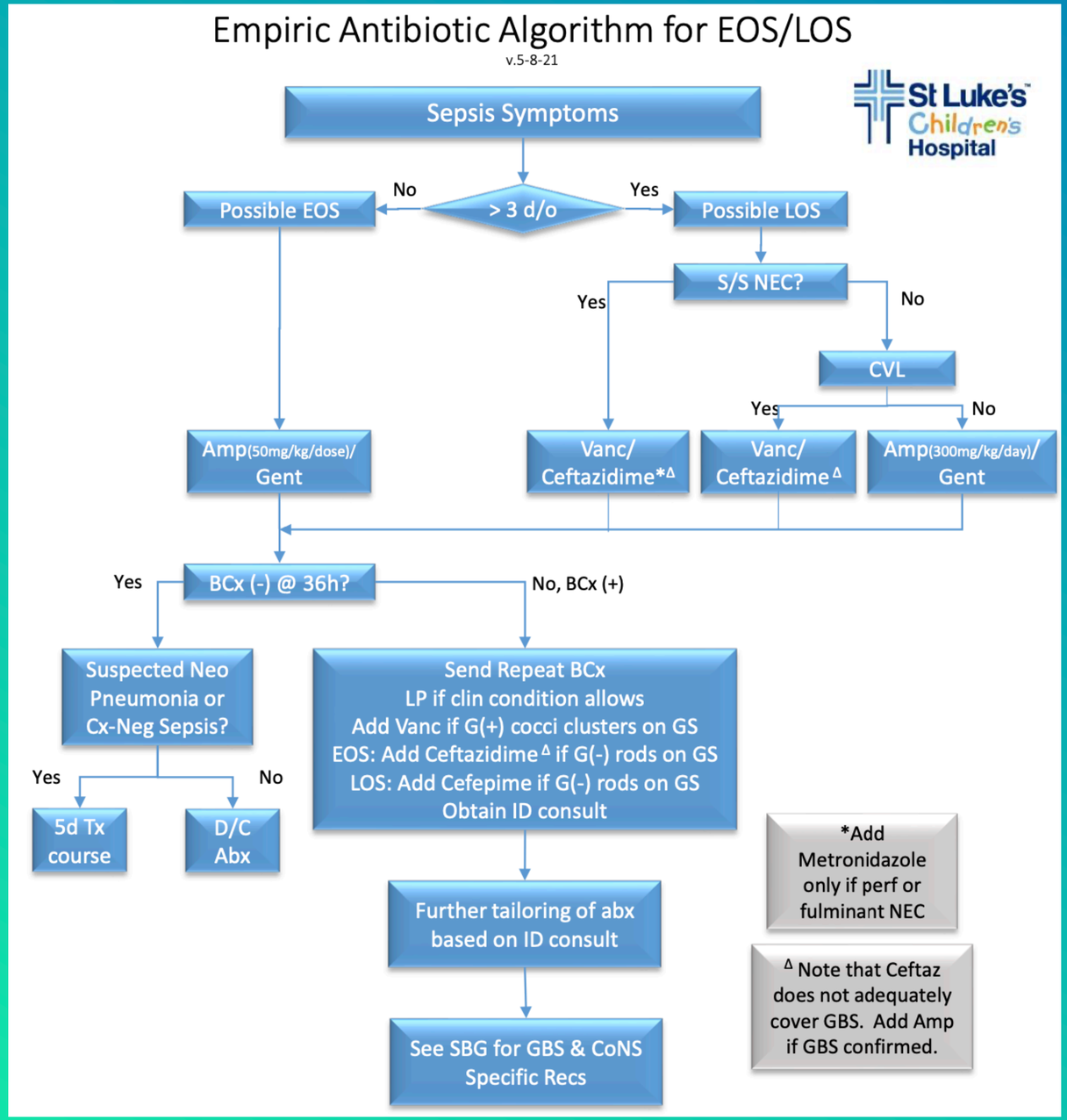
EOS

Treatment

- Ampicillin + aminoglycoside (gentamicin)
  - If severely ill, consider third/fourth cephalosporin addition
- E. coli is the leading pathogen for death associated with antibiotic resistance
- Ampicillin and gentamicin should provide optimal coverage for more than 90% EOS cases
- Prophylactic fluconazole in preterm infants (<1Kg with central line)

EOS

Treatment



Late Onset Sepsis

Definition

- Majority preterm infants
- Onset of symptoms >72 hours of age (>7 days?)
- Percentage of deaths attributed to infection increases with postnatal age
  - As high as 50% between days 15-28
- Clinical syndrome characterized by systemic signs of infection
- Almost impossible to distinguish sepsis from meningitis in newborn
  - Positive blood culture = bacteremia
  - Negative blood culture = clinical sepsis (if clinical features present)

LOS

Diagnosis

- ALARMING FACT:
  - For each confirmed case of infection, between 11 to 23 uninfected newborns are treated
  - Inadvertent use/overuse of antimicrobials can produce changes in newborn infant flora favoring emergence of multi-drug resistant bacteria
    - Empiric antibiotic treatment results in a threefold increase in risk of infection from resistant bacteria for every day of ampicillin and gentamicin use and up to 34 fold increase with cephalosporins use

LOS

Clinical Diagnosis

- Clinical manifestations:
  - Temperature instability (hyper/hypothermia)
  - Poor peripheral perfusion (beware warm shock!!)
  - Elevated direct bilirubin
  - Increased apnea/bradycardia events
  - Feeding intolerance/abdominal distention/bloody stools
  - Increased respiratory support
  - Lethargy
  - Hypotonia
  - Central line?

Environmental Factors

- Invasive medical devices
- Care providers
- NICU environment & surfaces

Host factors

- Gestational age
- IUGR
- Critical illness/ Comorbidities
- Delayed enteral feeds/ Parenteral nutrition
- Surgical treatment
- Length of hospital stay
- Host immune function
- Microbial colonization/ Microbiome
- Genetics

Late Onset Sepsis

Clinical Signs

Systemic	Temperature instability Feeding intolerance
Cardiorespiratory	Tachycardia/Bradycardia Hypotension/Poor perfusion Apnea/Tachypnoea/Dyspnoea FiO_2 ↑/Need for ventilator
CNS	Lethargy/Muscular hypotonia Seizures

Pathogens

- Gram-negative bacteria
- Gram-positive bacteria
- Fungi
- Viruses
- Multi-resistant microorganisms

Associated Infections

- Pneumonia
- Urinary tract infection
- Skin / soft tissue infection
- Necrotizing enterocolitis (NEC)
- Meningitis

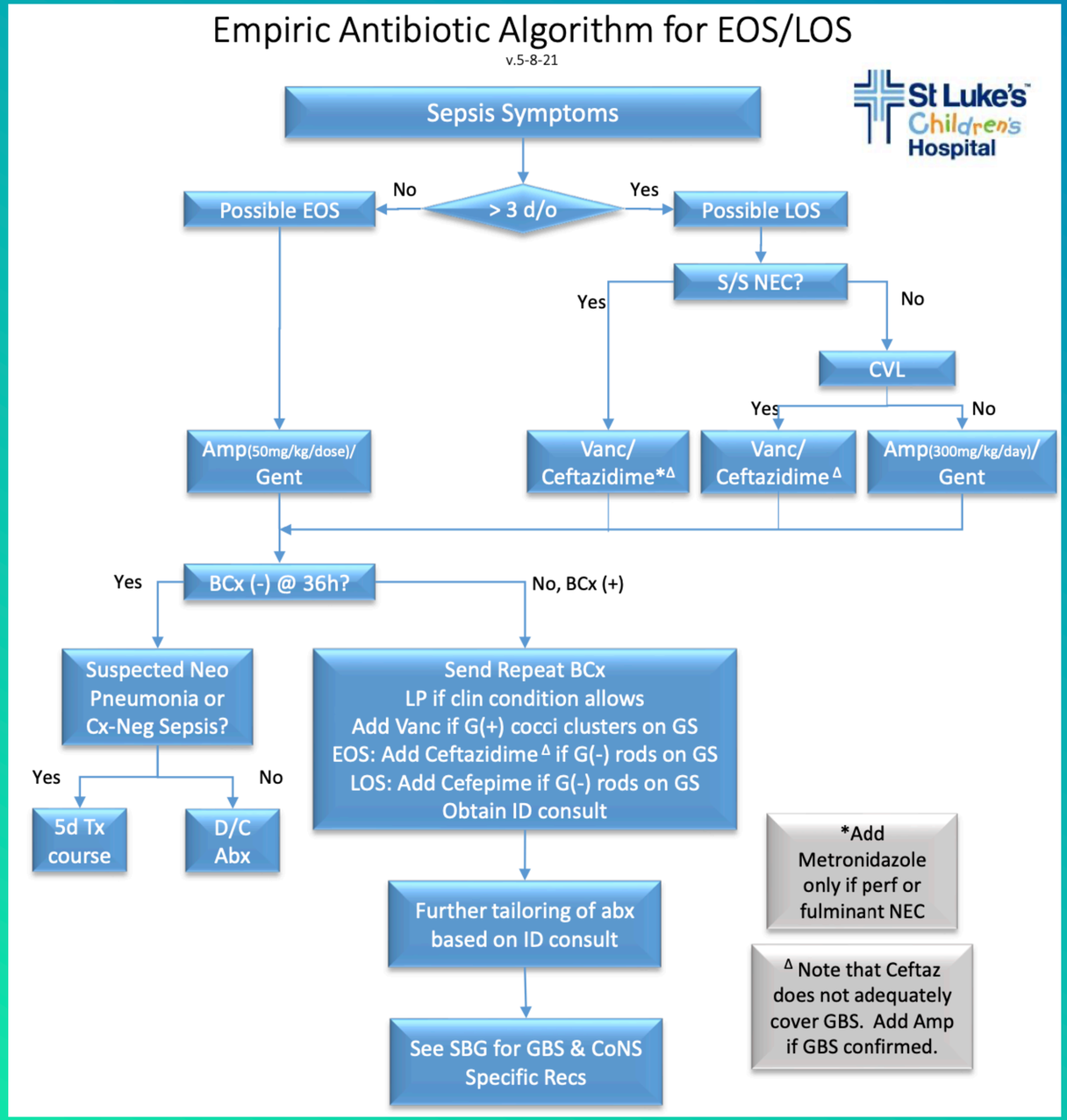
LOS

Laboratory Diagnosis

- Positive blood culture = gold standard
  - If central line, need blood culture x2 (one from the central line)
- LP is standard of care in LOS
  - Difficulty in diagnosing meningitis from CSF
    - Traumatic tap
    - Variability of normal cytologic and biochemical variables in neonate
- Urine culture/UA
- CBC, CRP?

LOS

Treatment



LOS

Prognosis

- Fungal/gram negative sepsis have higher death rates than gram positive
  - Shock more common with gram negative/fungal

LOS

Prognosis

- Fungal sepsis prognosis is poor
  - Higher mortality, higher incidence of CP, poor neurodevelopment outcomes
- Infected neonates present with hypotension, respiratory insufficiency, and hypoxemia that may compromise cerebral blood flow
- Per Bayley Scales of Infant Development for infants <30 weeks
  - At one year CGA, LOS is an independent predictor of poor prognosis
    - Delayed motor/mental development, CP