Do We Have This? A Neonatal and Pediatric Emergency Toolkit

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The speaker has no conflicts of interest to disclose.

Learning Objectives - Pharmacist

- Summarize the antibiotics recommended for neonatal sepsis and the importance of having them available for urgent administration once a patient is identified
- Describe the pathophysiology of ductal dependent congenital heart disease and the need for immediate administration of alprostadil
- Discuss the recommendations for zidovudine therapy in neonates born with maternal HIV exposure

Patient case

SB is a 3 day old female presenting to the emergency room with "lethargy and slow breathing". The delivery was without complications and after a 40 hour hospital stay, the neonate at the mother were discharged home. After the first night at home, the mother noted increased sleepiness and disinterest in feeding. Once the slow breathing was noted, the family contacted the pediatrician and was told to immediately bring the baby to the emergency room.

Neonatal and Pediatric Sepsis

Neonatal sepsis patient presentation

Which are symptoms of neonatal sepsis?

A. lethargy
B. hypothermia
C. seizures
D. all of the above

Neonatal sepsis patient presentation

- Hyper/hypothermia
- Brady/tachycardia
- Grunting
- Apnea
- Cyanosis
- Lethargy
- Irritability
- Anorexia
- Vomiting
- Jaundice
- Abdominal distension
- Diarrhea
- Absence of meningitis specific symptoms*

American Academy of Pediatrics. Serious Bacterial Infections Caused by *Enterobacteriaceae* (With Emphasis on Septicemia and Meningitis in Neonates) In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018: Accessed August 6, 2018.

Neonatal sepsis pathogens

The most common neonatal sepsis pathogens are

A. *S. pneumoniae* and *N. meningitidis*
B. Group B Streptococcus, *E. coli*, *L. monocytogenes*
C. *S. aureus* and *P. aeruoginosa*
D. Cryptococcus and Fusarium

Neonatal sepsis pathogens

- Group B streptococcus
  - *Streptococcus agalactiae*
  - Primary gram positive pathogen
  - Maternal testing prior to delivery
  - Prophylactic antibiotics for mother do not completely rule out acquisition
- *Escherichia Coli*
  - Major gram negative pathogen for neonatal sepsis
  - Higher risk in patients with maternal chorioamnionitis, low birth weight, birth prior to 37 weeks gestation, and prolong rupture of membranes

American Academy of Pediatrics. Group B Streptococcal Infections. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018: Accessed August 6, 2018.
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Neonatal sepsis pathogens

- *Listeria monocytogenes*
  - Primarily a foodborne transmission to the mother
    - Ready to eat lunch meat and hot dogs
    - Products made from unpasteurized milk
    - Sprouts
  - Gram positive rod, facultative anaerobe
  - Still considered a pathogen but "common" perhaps not

Mischler et al. Epidemiology of Bacteremia in Previously Healthy Febrile Infants: A Follow-up Study. Hospital Pediatrics 2015;5(6):293-300.

American Academy of Pediatrics. Serious Bacterial Infections Caused by *Enterobacteriaceae* (With Emphasis on Septicemia and Meningitis in Neonates). In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018: Accessed August 6, 2018

Early onset sepsis vs. late onset sepsis

Early onset sepsis
- Less than 72 hours from birth
- More likely to be associated with pathogens from the birth canal

- Late onset sepsis
  - More than 72 hours from birth
  - Extends through 8-12 weeks of age
  - May still include birth canal pathogens
  - Increased risk of S. pneumoniae, S. aureus
  - Commonly associated with line infection, prolonged hospitalization

Empiric antibiotic regimen

What would be an appropriate empiric antibiotic regimen for this patient?

A. ceftriaxone
B. ampicillin and cefotaxime
C. vancomycin and cefepime
D. ampicillin and gentamicin
E. B and D

Neonatal concerns with ceftriaxone

- Does not cover L. monocytogenes
- Displaces bilirubin from plasma protein
  - Increased risk of hyperbilirubinemia
  - Increased risk of gall bladder disorders
- Chelates with ionized calcium in soft tissues
  - Deposits stone in kidneys and lungs
  - Can result in organ dysfunction and death

Bradley et al. Intravenous Ceftriaxone and Calcium in the Neonate: Assessing the Risk for Cardiopulmonary Adverse Events. Pediatrics 2009;123:e609–e613

Empiric Antibiotic Regimen

- Ampicillin & gentamicin
  - Covers major early onset neonatal sepsis pathogens
  - Be aware of your antibiogram – does gentamicin cover E. Coli in your area?
  - Does require therapeutic drug monitoring (TDM) if continued beyond 48 hours
  - Has reasonable CNS penetration due to a immature blood brain barrier
- Ampicillin & cefotaxime
  - Covers major early onset neonatal sepsis pathogens
  - More consistent coverage against E. coli
  - Better supportive data for CNS penetration

American Academy of Pediatrics. Group B Streptococcal Infections. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018: Accessed August 6, 2018.

American Academy of Pediatrics. Serious Bacterial Infections Caused by *Enterobacteriaceae* (With Emphasis on Septicemia and Meningitis in Neonates). In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018: Accessed August 6, 2018.

Drug shortages – of course!

Cefotaxime – on ASHP shortage list since 2013

- Hospira stopped making cefotaxime
- Baxter stopped making cefotaxime
- Sanofi-Aventis stopped making cefotaxime
- Hikma Pharmaceutical (West Ward) – has raw material and demand issues
  - Long term back order
  - No release date

Wheeler, M. July 5th, 2018. Cefotaxime sodium injection. ASHP Current Drug Shortages. Accessed from www.ashp.org/drug-shortages

Substitutions for neonatal sepsis

- American Academy of Pediatrics Recommendation
  - Use ceftazidime in place of cefotaxime
- When can we use ceftriaxone safely
  - Patients over 28 days of age

Alternatives to consider during cefotaxime shortage. AAP News Feb 2015, E150225-1

Survey

In your facility

A. Ampicillin and ceftazidime/cefotaxime are compounded and sent by pharmacy 24/7
B. Ampicillin and ceftazidime/cefotaxime are available in Pyxis and compounded by nursing staff
C. Ampicillin and ceftazidime/cefotaxime are available in an after hours cabinet / room and compounded by nursing staff
D. Ampicillin or cefotaxime/ceftazidime are not stocked in an accessible place for urgent/emergent use

Recommendations for Pediatric Sepsis

- No national guidelines
- Institution specific recommendations
- Usually related to a primary disease state
  - Pneumonia
  - Meningitis – with symptoms
  - UTI
  - Abdominal infection
- Integrate local antibiogram data into empiric therapy choices

Outside Support / Forcing Functions

Gabby's Law

- In effect in August 2016
- Requires hospitals to:
  - Implement an evidence-based process for quickly recognizing and treating adults and children with sepsis
  - Train hospital staff to identify and treat patients with possible sepsis
  - Collect sepsis data to improve care and provide it to the state

Outside Support / Forcing Functions

IDPH

- Suggest pediatric sepsis quality indicators
  - Sepsis screening protocols, triggers, order sets
  - IV access and fluid bolus within 20 minutes of recognition of sepsis
  - Antibiotic administration within first hour (or defined timeframe per institution)

A new wrinkle to our case…

SB is admitted for spinal tap and antibiotics. As the baby was being prepped for the spinal tap, the baby developed tachycardia and hypotension. Cyanosis was noted by the medical team.

Emergent Presentation of Congential Heart Disease

Fetal Circulation

- Blood is oxygenated by the placenta
- Lungs are bypassed when utero
- After birth, ductus arteriosus and foramen ovale close
  - Changing pressures
  - Exposure to oxygen
  - Decreased exposure to prostaglandins

Congenital Heart Disease (CHD)

- 60-70% of patients have diagnosed CHD prior to delivery
- Leading cause of birth defect-associated illness and death in infants
- Risk of heart defects increased with early-onset (< 34 weeks) preeclampsia, preeclampsia with growth restriction, and severe preeclampsia
- Associated with multiple genetic disorders

Landis, Bi et al (2013). Prenatal Diagnosis of Congenital Heart Disease and Birth Outcomes. *Pediatric Cardiology*, 34(3), 597–605.

Auger N et al. Association Between Preeclampsia and Congenital Heart Defects. JAMA. 2015 Oct 20;314(15):1588-98

Bruneau BG. Genetics of congenital heart disease. Curr Cardiol Rev. 2010 May;6(2):91-7.

Congenital Heart Disease

Cyanotic Heart Lesions
- Tricuspid/Pulmonary Atresia (DD)
- Transposition of the Great Vessels (DD)
- Tetralogy of Fallot (DD*)
- Total Anomalous Pulmonary Return (DD)
- Hypoplastic Left Heart Syndrome (DD)
- Truncus Arteriosus

Non-cyanotic Heart Lesions
- Atrial Septal Defect
- Ventricular Septal Defect
- Pulmonary Stenosis (DD*)
- Coarctation of the Aorta (DD*)
- Patent Ductus Arteriosus

DD = ductal dependent

DD*= ductal dependent physiology based

Treatment

- Stabilization and referral
- Prostaglandins to keep the ductus arteriosus open
- Alprostadil – prostaglandin E_1
  - 0.05 – 0.1 mcg/kg/min by continuous infusion
    - Titrate to effect doses of 0.01-0.4 mcg/kg/min reported
  - Common side effects – apnea, hypotension
  - Prepare to a concentration of 10mcg/ml (per VON, ISMP)
  - Refrigerated, comes as a 500mcg/ml ampule
  - NIOSH list
  - Intermittent shortages / back order

Survey

A. My facility stocks alprostadil and I know where to find it
B. My facility stocks alprostadil and I don't know where to find it
C. My facility does not stock alprostadil
D. I'm not sure if my facility stocks this

Survey

A. My facility has a standard dilution / order set in which to order alprostadil drips if necessary
B. My facility does not have a standard dilution / order set in which to order alprostadil drips if necessary
C. I don't know

Alprostadil acquisition ideas

- $700 for a box of 5 ampules
- Use system resources – split a box
- Confirm that any transport is bringing drug to the site

Maternal HIV Transmission

Patient Case

A woman presents to the emergency room in advanced stages of labor. She has not had any prenatal care. The rapid HIV test comes back positive and it apparent that she is going to deliver prior to transfer to the tertiary referral center.

Intrapartum Management

- If there's time…
- Intravenous zidovudine
  - Should be administered to women with HIV RNA >1,000 copies/mL or unknown HIV RNA
  - May be considered in women with HIV RNA between 50 and 99 copies/mL
  - Dose: 2mg/kg/load, 1mg/kg/hour continuous infusion until cord clamp

Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Transmission in the United States. Available at http://aidsinfo.nih.gov/contentfiles/lyguidelines/PerinatalGL.pdf. Accessed August 16th, 2018.

Two sets of guidelines for neonatal therapy

- Department of Health and Human Services
  - aidsinfo.nih.gov
- Illinois Perinatal HIV Hotline
  - 800-439-4079

- Either set of guidelines can be used

Risk levels regarding perinatal transmission – HHS Guidelines

High Risk

- Mothers who received neither antepartum nor intrapartum ARV drugs
- Mothers who received only intrapartum ARV drugs
- Mothers who received antepartum and intrapartum ARV drugs but who have detectable viral load near delivery, particularly if delivery was vaginal
- Mothers with acute or primary HIV infection during pregnancy or breastfeeding

Low Risk

- Mothers received standard ART during pregnancy with sustained viral suppression near delivery and no concerns related to adherence

Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Transmission in the United States. Available at http://aidsinfo.nih.gov/contentfiles/lyguidelines/PerinatalGL.pdf. Accessed August 16th, 2018.

Neonatal Treatment Guidelines – HHS Guidelines

- High Risk
  - 6 weeks of therapy
  - Two options
    - Zidovudine – 4mg/kg/dose PO BID
    - Nevirapine x 3 doses
      - 12mg (not weight based)
      - 2 doses 48 hours apart, one dose 96 hours after second dose

    Or
    - 3 drug regimen
      - Zidovudine 4mg/kg/dose PO BID
      - Lamivudine 2mg/kg/dose PO BID
      - Nevirapine 6mg/kg/dose PO BID
- Low Risk
  - 4 weeks of therapy
  - Zidovudine 4mg/kg/dose PO BID

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Risk levels regarding perinatal transmission – Illinois Perinatal HIV Hotline

High risk

- Infants born < 33 weeks gestation
- Infants born to women whose HIV viral load was detectable (anything greater than 20 copies/mL) after 28 0/7 weeks gestation
- Infants born to women who did not receive antepartum antiretroviral therapy
- Infants born to women who started antiretroviral therapy after 13 0/7 weeks gestation
- Infants born to women who became infected with HIV or seroconverted during pregnancy
- Infants born to women diagnosed with HIV during labor or postpartum

Low risk

- All other infants

Hotline Best Practices for Care of Infants with Perinatal Exposure to HIV. (April 2017). Retrieved from http://www.hivpregnancyhotline.org/content/resource/hotline-best-practices-care-infants-perinatal-exposure-hiv.

Neonatal Treatment Guidelines – Illinois Perinatal HIV Hotline

High Risk

- Zidovudine 4mg/kg/dose PO BID x 6 weeks
- Lamivudine 2mg/kg/dose PO BID – duration dependent on neonatal HIV PCR results
- Nevirapine 6mg/kg/dose PO BID – duration dependent on neonatal HIV PCR results

Low Risk

- 4 weeks therapy
- Goal of zidovudine administration in the first hour after delivery
- 4mg/kg/dose PO BID

Or

- 2-2.9ml – 1ml PO BID
- 3-3.9ml – 1.5ml PO BID
- 4-4.9ml – 2ml PO BID

Hotline Best Practices for Care of Infants with Perinatal Exposure to HIV. (April 2017). Retrieved from http://www.hivpregnancyhotline.org/content/resource/hotline-best-practices-care-infants-perinatal-exposure-hiv.

What to keep and how much?

- Zidovudine for injection - $35 / vial ($350 for 10 pack)
- Zidovudine for oral solution - $80 / bottle
- Lamivudine (Epivir) - $120 / bottle
- Nevirapine (Viramune) - $223 / bottle

What is the best perinatal treatment for the neonate in our patient case?

A. No therapy needed
B. Zidovudine 4mg/kg/dose PO BID x 4 weeks
C. Zidovudine 4mg/kg/dose PO BID x 6 weeks
D. Zidovudine 4mg/kg/dose PO BID x 6 weeks, plus lamivudine and nevirapine

Survey

A. My institution has a clinical guideline or order set available for neonatal HIV prophylaxis and has all medications available
B. My institution has a clinical guidelines or order set available for neonatal HIV prophylaxis and does not have all medications available
C. My institution does not have a clinical guideline or order set for neonatal HIV prophylaxis

Caring for pediatric patients

- Individualized pediatric doses
- Manipulation of commercially available products
- More likely to be on the receiving end of a dosing error
- Newly available pediatric dosage forms retain brand

Training to care for pediatric patients

- Competencies for pharmacists and nurses that may care for pediatric patients
- Simulation and drill emergent/urgent situations
- Orientation on where urgently needed and not often used products are stored

Questions?