



PEDIATRICS FOR THE NON-PEDIATRIC PHARMACIST

Jerrica Eaton, PharmD & Taylor Mathwich, PharmD

Clinical Pharmacists

Children's of Alabama



DISCLOSURES

No conflict of interest to disclose

OBJECTIVES

- Recognize appropriate use of direct oral anticoagulants in specific patient populations
- Evaluate evidence for the use of direct oral anticoagulants in pediatric patients
- Review the pathophysiology and treatment of neonatal sepsis
- Discuss the clinical presentation and treatment of well-appearing febrile infants



ANTICOAGULATION IN PEDIATRIC PATIENTS

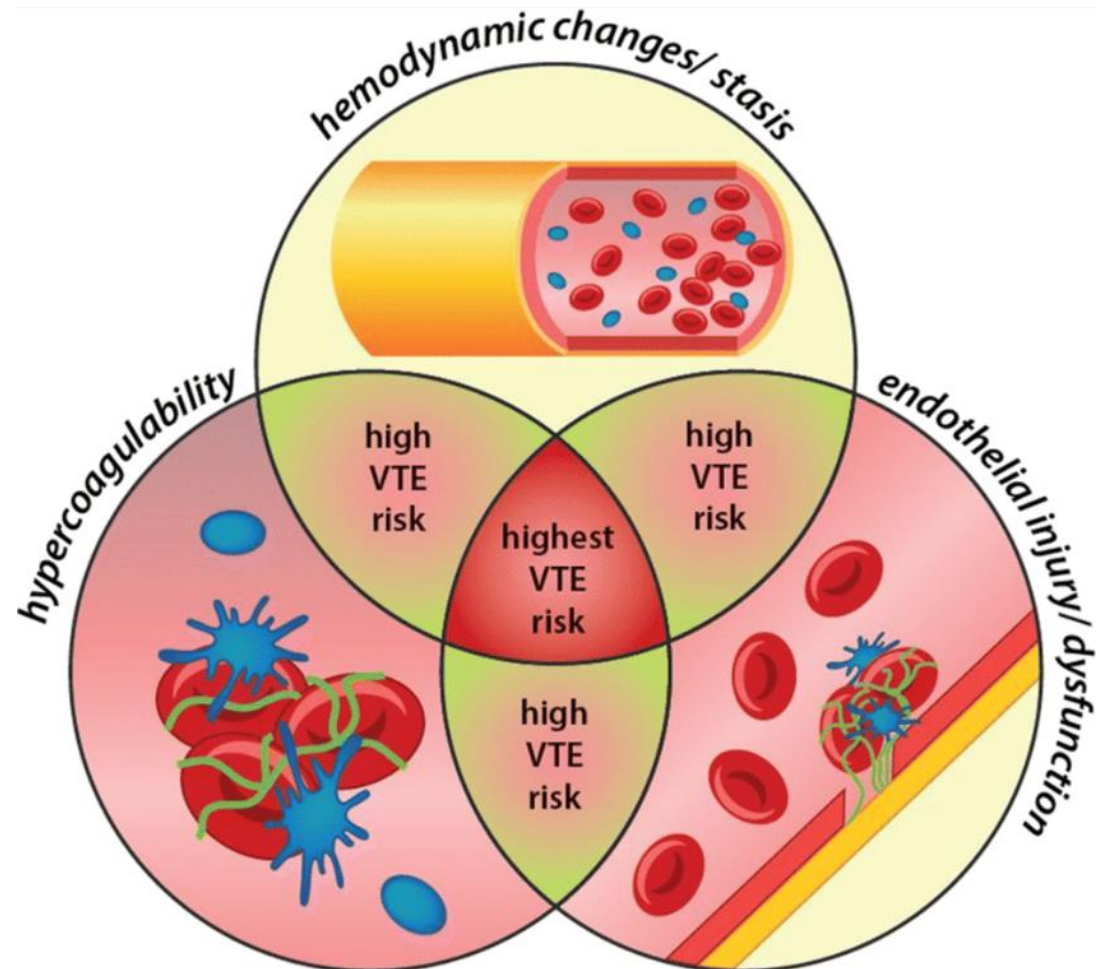


EPIDEMIOLOGY

- Incidence: 1-5 per 100,000 children per year
- Increased trend in the diagnosis of venous thromboembolism in pediatric patients
 - Increasing clinical recognition and reporting
 - Increased use of central venous catheters

PEDIATRIC SPECIFIC RISK FACTORS

- Developmental homeostasis
- Low antithrombin levels in during infancy
 - 50-75% of adult levels
 - Adult levels of antithrombin at 6-12 months of age



ANTICOAGULANTS WITH FDA APPROVAL FOR PEDIATRIC PATIENTS

Parenteral

*Unfractionated Heparin

*Enoxaparin
(Low Molecular Weight Heparin)

Oral

Rivaroxaban

Dabigatran

*Warfarin

*Recommended as an anticoagulant of choice by the 2018 American Society of Hematology Pediatric Venous Thrombosis Guidelines

Monagle P, et al. *Blood Adv.* 2018;2:3292-3316.
Pinchinat A, et al. *Blood* 2019; 134 (Supplement_1): 2443.
Male C, et al. *Lancet Haematol* 2020;7:e18-27.
Halton J, et al. *Lancet Haematol* 2021;8:e22-23.

UNFRACTIONATED HEPARIN

- Mechanism of Action: Potentiates antithrombin III, inactivates factors II, IXa, Xa, XIa, XIIa, prevents conversion of fibrinogen to fibrin
- Contraindications: Active bleeding, hypersensitivity to pork, malignant hypertension, heparin-induced thrombocytopenia
- Pharmacokinetics: Shorter half-life in neonates
- Management: Goal anti-Xa for treatment: 0.3-0.6 units/mL
- Special considerations:
 - High bilirubin can falsely lower anti-Xa level
 - May cause hyperkalemia
 - Can decrease bone density
 - Heparin resistance

Treatment Dosing of Heparin at COA

| | |
|---------------------------|---|
| Loading dose | 75 units/kg (max: 8,000 units) |
| Infusion rate | 18-28 units/kg/hr |
| Supplemental bolus | Anti-Xa <0.2 units/mL: 75 units/kg (max: 8,000 units) |
| | Anti-Xa 0.2-0.29 units/mL: 40 units/kg (max: 8,000 units) |

ENOXAPARIN

- Mechanism of Action: Inhibits Factor Xa via Antithrombin III
- Contraindications: Active major bleeding, hypersensitivity to enoxaparin, heparin, pork, heparin-induced thrombocytopenia
- Pharmacokinetics:
 - Obesity increases volume of distribution
 - Hepatically metabolized via desulfation and depolymerization
 - Renally excreted
- Management:
 - Goal anti-Xa for treatment: 0.5-1 units/mL
 - Goal anti-Xa for prophylaxis: 0.2-0.4 units/mL
- Special considerations:
 - Heparin resistance
 - Prefilled syringes versus multi-dose vial
 - Hyperkalemia

| Treatment Dosing of Enoxaparin at COA | |
|---------------------------------------|--|
| Premature, <1 month | 2 mg/kg/dose q12h |
| Term, <1 month | 1.7 mg/kg/dose q12h |
| 1 month to <2 months | 1.5 mg/kg/dose q12h |
| ≥2 months | 1 mg/kg/dose q12h (max: 150 mg/dose) |
| >12 years old & >50 kg | 1.5 mg/kg/dose q24h*** (max: 225 mg/dose) |
| ***Goal anti-Xa level: 1-2 units/mL | |

RIVAROXABAN

- Mechanism of Action: Factor Xa inhibitor
- Contraindications: Severe renal failure, moderate to severe liver dysfunction, CYP3A4/P-gp inducers/inhibitors, NPO status
- Pharmacokinetics:
 - Metabolized by CYP3A4, substrate of P-gp
 - Absorption dependent on site of drug release
- Management: Levels not routinely obtained
- Special considerations:
 - Minimum of 5 days of parenteral therapy
 - Take with meal
 - Can crush tablet, but not split
 - Available as an oral solution

RIVAROXABAN DOSING FOR TREATMENT OF VTE

| Weight | Dose |
|------------|-----------------|
| 2.6-2.9 kg | 0.8 mg/dose q8h |
| 3-3.9 kg | 0.9 mg/dose q8h |
| 4-4.9 kg | 1.4 mg/dose q8h |
| 5-6.9 kg | 1.6 mg/dose q8h |
| 7-7.9 kg | 1.8 mg/dose q8h |
| 8-8.9 kg | 2.4 mg/dose q8h |
| 9-9.9 kg | 2.8 mg/dose q8h |
| 10-11.9 kg | 3 mg/dose q8h |
| 12-29.9 kg | 5 mg/dose q12h |
| 30-49.9 kg | 15 mg/dose q24h |
| ≥50 kg | 20 mg/dose q24h |

EINSTEIN JR PHASE III TRIAL

Population

- 0-17 years old with acute VTE & completed at least 5 days of heparin
- If <6 months: >37 gestational age at birth, >2.6 kg, feeding orally for at least 10 days

Treatment

- Rivaroxaban
- Standard anticoagulants: UFH, LMWH, Vitamin K Antagonist

Efficacy

- **Symptomatic Recurrent VTE**
- Rivaroxaban: 4/335 (1%)
- Standard: 5/165 (3%)

Limitations

- Only 25% of patients had catheter-related thrombosis
- Birth-23 months was not well represented
- Higher rates of menorrhagia with rivaroxaban

APIXABAN

- Not currently indicated for use in pediatric patients
- Mechanism of Action: Factor Xa inhibitor
- Contraindications: Severe renal impairment, moderate to severe liver dysfunction, CYP3A4/P-gp inducers/inhibitors
- Pharmacokinetics: Metabolized via CYP3A4/5, substrate of P-gp
- Management: Levels not routinely obtained
- Special considerations:
 - Can crush tablets
 - May suspend in water, D5W, apple juice, apple sauce

| Adult Dosing | |
|----------------------------------|----------------------------------|
| Atrial Fibrillation | 5 mg BID |
| Venous Thromboembolism | 10 mg BID x7 days, then 5 mg BID |
| Heparin-Induced Thrombocytopenia | 10 mg BID x7 days, then 5 mg BID |

DABIGATRAN

- Mechanism of Action: Direct thrombin inhibitor
- Contraindications: Hypersensitivity, mechanical prosthetic valves
- Pharmacokinetics:
 - Excreted in the urine
 - Metabolized by hepatic esterases
- Management: Levels not routinely obtained
- Special considerations:
 - Minimum of 5 days of parenteral therapy
 - Do not open capsules and give with full glass of water
 - Do not give oral pellets via G-tube

DIVERSITY PHASE IIb/III TRIAL

Population

- 0-17 years with acute VTE who completed at least 5 days of parenteral therapy & expected to need anticoagulation for 3 months
- If <2 years: >37 weeks gestational age at birth & weight >3rd percentile

Treatment

- Dabigatran
- Standard anticoagulants: LMWH, UFH, VKA, fondaparinux

Efficacy

Complete Thrombus Resolution

- Dabigatran: 81/177 (46%)
- Standard: 38/90 (42%)
- Non-Inferiority P Value: <0.0001

Limitations

- Complex dosing
- Underrepresentation of <2 years, central line thrombosis, cancer
- High use of VKA
- Pellets and oral suspension not currently commercially available

REVERSAL AGENTS

| Reversal Agent | Drug Reversed | FDA Approved in Pediatrics |
|---------------------------------|-----------------------|----------------------------|
| Protamine | Heparin, enoxaparin | No |
| Andexxa (Recombinant Factor Xa) | Rivaroxaban, apixaban | No |
| Praxbind (idarucizumab) | Dabigatran | No |

Protamine [prescribing information]. Lake Zurich, IL: Fresenius Kabi; December 2016.

Andexxa (andexanet alfa) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; July 2022.

Praxbind injection (idarucizumab) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc; October 2021.

CURRENT STUDIES

- Apixaban:
 - Apixaban for the Acute Treatment of Venous Thromboembolism in Children
 - PREVAPIX-ALL: Apixaban Compared to Standard of Care for Prevention of Venous Thrombosis in Paediatric Acute Lymphoblastic Leukemia
 - Safety of ApiXaban On Pediatric Heart disease On the prevention of Embolism (SAXOPHONE) study
- Rivaroxaban:
 - Comparison of the Efficacy of Rivaroxaban to Warfarin in Cerebral Venous Thrombosis
- Edoxaban:
 - Phase I Pediatric Pharmacokinetics/Pharmacodynamics (PK/PD) Study
 - Hokusai Study in Pediatric Patients With Confirmed Venous Thromboembolism

ASSESSMENT

- Which of the following anticoagulants are FDA approved for use in pediatric patients?
 - A. Apixaban
 - B. Rivaroxaban
 - C. Enoxaparin
 - D. B&C
 - E. All of the above



NEONATAL SEPSIS & FEBRILE INFANTS

OBJECTIVES

- Review the pathophysiology and treatment of neonatal sepsis
- Discuss the clinical presentation and treatment of well-appearing febrile infants

DEFINITIONS

Early Onset Sepsis

- Bacterial sepsis occurring within 72 hours of birth
- Usually vertically transmitted (from maternal bacteria in birth canal)

Late Onset Sepsis

- Bacterial sepsis with onset > 72 hours after birth
- Usually horizontally transmitted (through the community, healthcare workers while inpatient, or through surgery/procedures)

RISK FACTORS

Early Onset Sepsis

- Preterm Birth
- Maternal colonization with Group B Streptococcus (GBS)
- Prolonged rupture of membranes > 18 hours
- Intrapartum fever or chorioamnionitis

Late Onset Sepsis

- Surgical procedures
- Presence of IVs or catheters
- Prolonged hospital stay
- TPN/lipids (especially long term)
- Indwelling devices (shunts, any type of plastic)

CAUSES

Early Onset Sepsis

- Group B Streptococcus (GBS)
- E. coli
- S. aureus
- Listeria
- Ureaplasma
- Enterococcus

Late Onset Sepsis

- E. coli
- GBS
- Coagulase negative staphylococci (CONS)
- S. aureus
- Candida
- SPACE (Serratia, P. aeruginosa, Acinetobacter, Citrobacter, Enterobacter)

Pediatrics. 2018;142(6):e20182894.

Pediatrics. 2018;142(6):e20182896.

NeoReviews. 2012;13(2):e94-e102.

EVALUATION AND MANAGEMENT OF WELL APPEARING FEBRILE INFANTS

- The American Academy of Pediatrics (AAP) released the clinical practice guideline for Evaluation and Management of Well-Appearing Febrile Infants 8-60 Days Old
 - These recommendations do NOT apply to infants in their 1st week of life
- Recommendations are divided into algorithms based on patient age
 - Infants 8 to 21 days of age
 - Infants 22 to 28 days of age
 - Infants 29 to 60 days of age

LET'S DEFINE "WELL APPEARING"

Rectal temperature $\geq 38^{\circ}\text{C}$ or 100.4°F at home in the past 24 hours or in clinical setting

Gestation ≥ 37 weeks and < 42 weeks

8 to 60 days of age and at home after discharge from the hospital or born at home

ED Well-Appearing Febrile Infant Guideline

* EXCLUSION CRITERIA *

- Ill appearance
- Prematurity (<37 wga)
- Chronic medical problem
- Congenital or chromosomal abnormalities
- Confirmed/suspected immune compromise
- High suspicion for HSV (vesicles)
- Infants <2 weeks old with perinatal history of maternal fever, infection, or antimicrobial use
- Presence of focal bacterial infection (cellulitis, omphalitis, etc, but excluding AOM)
- Prior surgery or infection
- Immunizations in the last 48 hours

Table 1: HSV Risk & Treatment

HSV High-Risk Factors (High-risk if ≥1)

- Ill appearance
- Caregiver hx of cold sores or perioral HSV
- Maternal genital lesions +/- 48 hrs from delivery
- Maternal fever +/-48 hrs from delivery or chorioamnionitis
- Skin/mucus membrane vesicles or ulcers
- Seizures or altered mental status
- Hypothermia ≤96.8°F
- Abnormal labs (if obtained):
 - Transaminitis (elevated ALT or AST)
 - Thrombocytopenia
 - Leukopenia
 - CSF pleocytosis in the absence of a positive Gram stain result

HSV workup:

- Serum HSV PCR
- CSF HSV PCR
- HSV surface cultures AND PCR of:
 - Conjunctiva, nasopharynx, oral, anus
 - Any suspicious skin lesions

Table 2: Antimicrobials

- 0-21 days: Ampicillin + Gentamicin
- 22-28 days: Ceftriaxone monotherapy (add ampicillin if there is CSF pleocytosis)
- 29-60 days: Ceftriaxone monotherapy (add vanc if there is CSF pleocytosis)
- 0-42 days: Acyclovir if high-risk for HSV

Other Considerations:

- IM formulations available for all antibiotics and should be used to ensure treatment within 3 hours of arrival
- Antibiotics within 3 hours of arrival should be prioritized over prior LP if necessary

Review whether pt meets criteria (see exclusions to left)

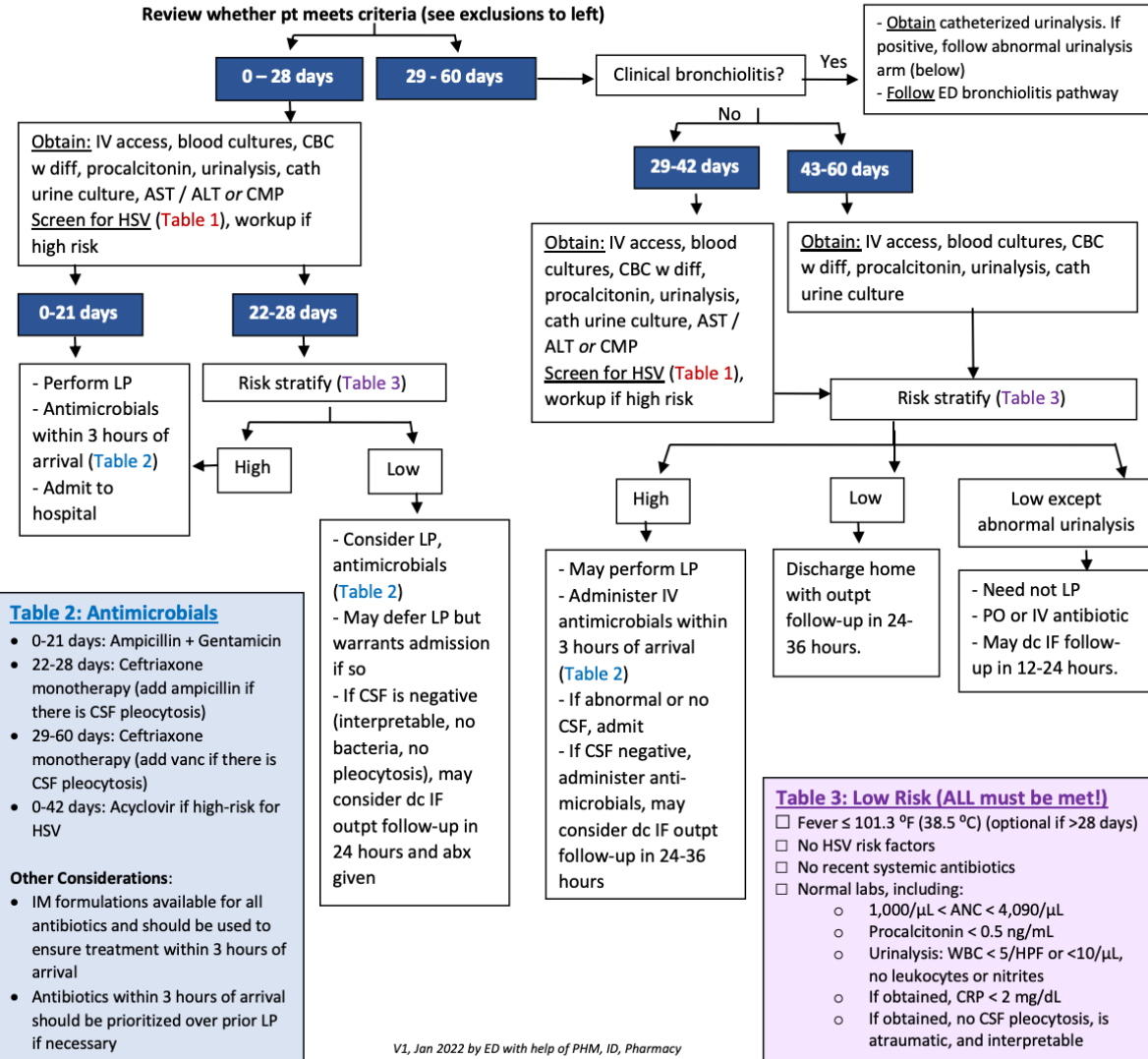


Table 3: Low Risk (ALL must be met!)

- Fever ≤ 101.3 °F (38.5 °C) (optional if >28 days)
- No HSV risk factors
- No recent systemic antibiotics
- Normal labs, including:
 - 1,000/μL < ANC < 4,090/μL
 - Procalcitonin < 0.5 ng/mL
 - Urinalysis: WBC < 5/HPF or <10/μL, no leukocytes or nitrites
 - If obtained, CRP < 2 mg/dL
 - If obtained, no CSF pleocytosis, is atraumatic, and interpretable

Work Up

Blood cultures

Complete Blood Count (CBC)

Procalcitonin

Urinalysis

Catheterized urine culture

AST/ALT or Complete Metabolic Panel (CMP)

Screen for Herpes Simplex Virus (HSV)

**INFANTS 0-28
DAYS**

HSV RISK ASSESSMENT

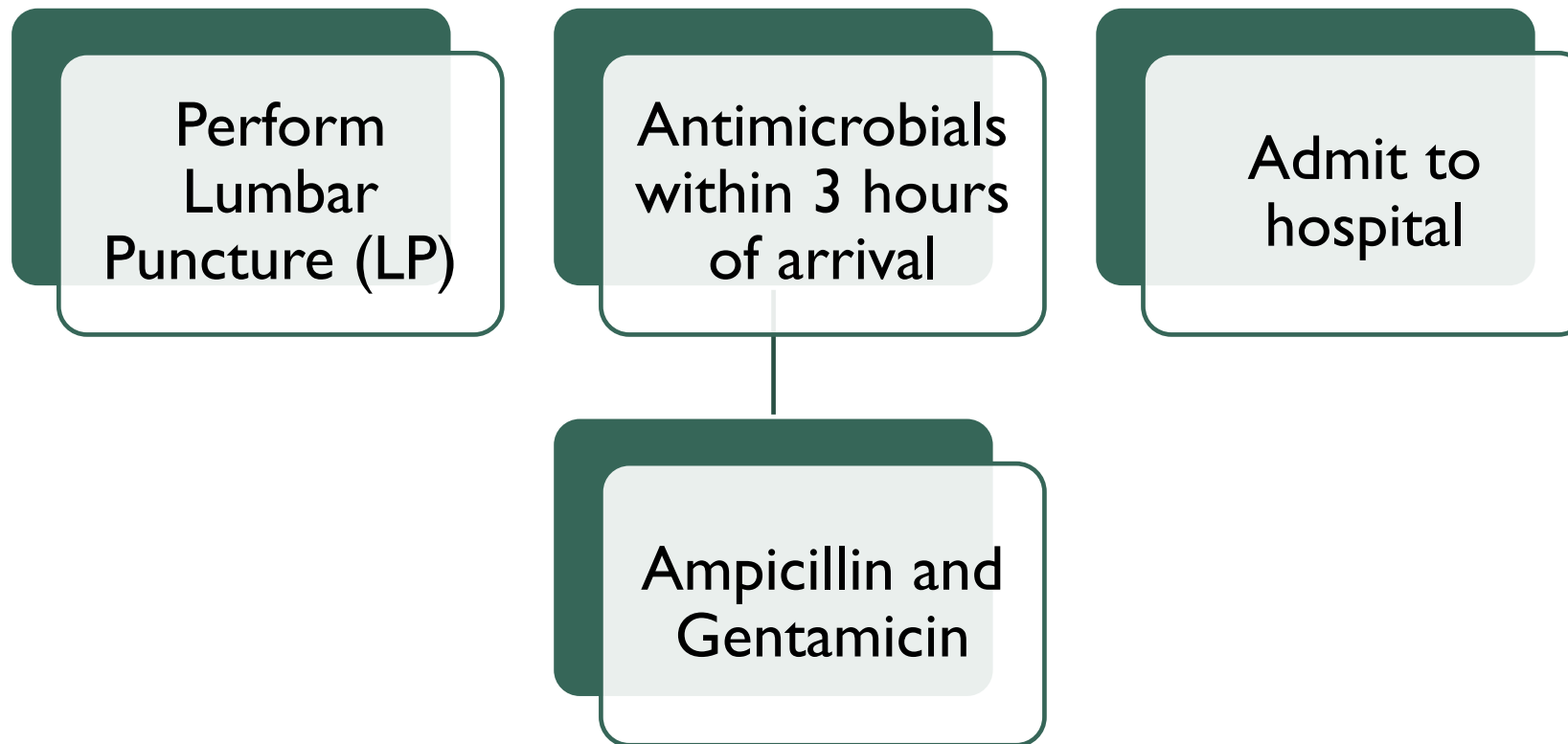
HSV Risk Factors

- High risk if ≥ 1 of the following:
 - Ill appearance
 - Caregiver history of cold sore or perioral HSV
 - Maternal genital lesions +/- 48 hours from delivery
 - Maternal fever +/- 48 hours from delivery or chorioamnionitis
 - Skin/mucus membrane vesicles or ulcers
 - Seizures or altered mental status
 - Hypothermia ≤ 96.8 F
 - Abnormal labs
 - Elevated ALT or AST, Thrombocytopenia, Leukopenia, CSF pleocytosis in the absence of a positive gram stain result

HSV Workup

- Serum HSV PCR
- CSF HSV PCR
- HSV Surface Cultures and PCR of:
 - Conjunctiva, nasopharynx, oral, anus
 - Any suspicious skin lesions

ALL INFANTS 0-21 DAYS



INFANTS 22-28 DAYS: STRATIFY RISK

-
- Low Risk (ALL criteria must be met)
 - Fever $\leq 101.3^{\circ}\text{F}$ (38.5°C)
 - No HSV risk factors
 - No recent systemic antibiotics
 - Normal labs, including:
 - $1,000/\mu\text{L} < \text{ANC} < 4,090/\mu\text{L}$
 - Procalcitonin $< 0.5 \text{ ng/mL}$
 - Urinalysis: WBC $< 5/\text{HPF}$ or $< 10/\mu\text{L}$, no leukocytes or nitrites
 - If obtained, CRP $< 2 \text{ mg/dL}$
 - If obtained, no CSF pleocytosis, is atraumatic, and interpretable

LOW RISK INFANTS 22-28 DAYS

- Consider LP
 - May defer LP, but warrants admission
- Antimicrobials within 3 hours of arrival
 - Ceftriaxone monotherapy
 - Add ampicillin if there is CSF pleocytosis
- If CSF is negative (interpretable, no bacteria, no pleocytosis) may consider discharge if outpatient follow up in 24 hours and antibiotics given

HIGH RISK INFANTS 22-28 DAYS

- Perform LP
- Antimicrobials within 3 hours of arrival
 - Ceftriaxone monotherapy
 - Add ampicillin if there is CSF pleocytosis
- Admit to hospital

INFANTS 29-60 DAYS

- Clinical Bronchiolitis?
 - Yes?
 - Obtain catheterized urinalysis. If positive, follow abnormal urinalysis arm
 - Treat bronchiolitis
 - No?
 - Age 29-42 Days
 - Obtain: IV access, blood cultures, CBC with differential, procalcitonin, urinalysis, cath urine culture, AST/ALT or CMP, screen for HSV and workup if high risk
 - Age 43-60 Days
 - Obtain: IV access, blood cultures, CBC with differential, procalcitonin, urinalysis, cath urine culture
 - Both age groups: Risk Stratify

HIGH RISK INFANTS 29-60 DAYS

- May perform LP
- Administer IV antimicrobials within 3 hours of arrival
 - Ceftriaxone monotherapy
 - Add vancomycin if there is CSF pleocytosis
- If abnormal or no CSF, admit to hospital
- If CSF negative, administer antimicrobials and consider discharge if outpatient follow-up in 24-36 hours

LOW RISK INFANTS 29-60 DAYS

- Discharge home with outpatient follow up in 24-36 hours
- Low risk except abnormal urinalysis
 - No need for LP
 - PO or IV antibiotic
 - May discharge if follow up in 12 to 24 hours

WHAT TO COVER?

- Gram negative organisms have been responsible for the majority of infections (60-80%) in infants <90 days old
 - E. coli is the most common pathogen
 - 70-90% of UTIs
 - 30-60% of bacteremia
 - 15-30% of bacterial meningitis
- Cephalosporins do NOT provide adequate coverage for Listeria or enterococci
 - When these organisms are suspected, use ampicillin

DOSING 8-21 DAYS OLD

| Suspected Source of Infection | 8-21 days old |
|-------------------------------|--|
| UTI | Ampicillin (IV or IM): 150 mg/kg/day divided every 8 hours AND Ceftazidime (IV or IM): 150 mg/kg/day divided every 8 hours or Gentamicin (IV or IM): 4 mg/kg/dose every 24 hours |
| No focus identified | Ampicillin (IV or IM): 150 mg/kg/day divided every 8 hours AND Ceftazidime (IV or IM): 150 mg/kg/day divided every 8 hours or Gentamicin (IV or IM): 4 mg/kg/dose every 24 hours |
| Bacterial Meningitis | Ampicillin (IV or IM): 300 mg/kg/day divided every 6 hours AND Ceftazidime (IV or IM): 150 mg/kg/day divided every 8 hours |

DOSING 22-28 DAYS OLD

| Suspected Source of Infection | 22-28 days old |
|-------------------------------|--|
| UTI | Ceftriaxone (IV or IM): 50 mg/kg/dose every 24 hours |
| No focus identified | Ceftriaxone (IV or IM): 50 mg/kg/dose every 24 hours |
| Bacterial Meningitis | Ampicillin (IV or IM): 300 mg/kg/day divided every 6 hours AND Ceftazidime (IV or IM): 150 mg/kg/day divided every 8 hours |

DOSING 29-60 DAYS OLD

| Suspected Source of Infection | 29-60 days old |
|-------------------------------|---|
| UTI | Ceftriaxone (IV or IM): 50 mg/kg/dose every 24 hours or Cephalexin (PO): 50-100 mg/kg/day in 4 divided doses or Cefixime (PO): 8 mg/kg/dose once daily |
| No focus identified | Ceftriaxone (IV or IM): 50 mg/kg/dose every 24 hours |
| Bacterial Meningitis | Ceftriaxone (IV): 100 mg/kg once daily or divided every 12 hours or Ceftazidime (IV): 150 mg/kg/day divided every 6 hours AND Vancomycin (IV): 60 mg/kg/day divided every 8 hours |

DURATION OF TREATMENT

- Discontinue parenteral antimicrobial agents and discharge hospitalized patients when all of the following are met:
 - Culture results are negative for 24-36 hours or only positive for contaminants
 - The infant continues to appear clinically well or improving (fever, feeding, etc.)
 - No other indications for hospitalization
- If patient has positive cultures, continue targeted antimicrobial therapy for the duration consistent with the nature of the disease, organism, and response to treatment

ASSESSMENT QUESTION

- JS is an 18 day old, 5 kg, ex 38 week gestation, male who presents with a temperature of 101°F. The team is concerned for bacterial meningitis. What would an appropriate antibiotic recommendation be based on the AAP Guidelines?
 - A. Ampicillin and Ceftazidime
 - B. Gentamicin
 - C. Vancomycin and Gentamicin

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ASSESSMENT QUESTION

- JS is an 18 day old, 5 kg, ex 38 week gestation, male who presents with a temperature of 101°F. The team is concerned for bacterial meningitis. You have recommended Ampicillin and Ceftazidime. The medical resident is now asking you, the pharmacist, what dose to give. Based on the AAP guideline recommendations, what would be an appropriate dosing regimen of ampicillin?
 - A. Ampicillin 1500 mg IV Q6H
 - B. Ampicillin 375 mg IV Q6H
 - C. Ampicillin 94 mg IV Q8H

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 - B. Ampicillin 375 mg IV Q6H
 - C. Ampicillin 94 mg IV Q8H

$$375 \text{ mg}/5 \text{ kg} = 75 \text{ mg/kg/dose} \times 4 = 300 \text{ mg/kg/day}$$



PEDIATRICS FOR THE NON-PEDIATRIC PHARMACIST

JERRICA EATON, PHARMD & TAYLOR MATHWICH, PHARMD

CLINICAL PHARMACISTS

CHILDREN'S OF ALABAMA

