Pediatric Potpourri

Recent Updates in Pediatric Pharmacotherapy

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Conflicts of Interest

- None to disclose

Objectives

- At the completion of this activity, **pharmacists** will be able to:
  - Calculate age appropriate doses of drugs using basic principles of developmental pharmacology
  - Apply recent data related to medication adverse events in pediatrics to specific clinical scenarios
  - Identify gaps that exist in data related to antimicrobial stewardship in hospitalized children
- At the completion of this activity, **pharmacy technicians** will be able to:
  - List three fundamental differences between pediatric and adult patients regarding drug therapy
  - Describe emerging concerns regarding proton pump inhibitors in infants
  - Recognize infections in children where short durations of treatment are appropriate

DRUG DOSING IN PEDIATRICS

BASICS OF AGE-APPROPRIATE DOSING

CONSIDERATION OF PATIENT AND DRUG-SPECIFIC VARIABLES

Caring for Hospitalized Children

- **71%** of all pediatric hospitalizations in the United States occurred at general hospitals that treat both adult and pediatric patients (Leyenaar, 2016)
- Wide variability of pediatric education within required curricula and post-graduate training (Prescott, 2014)
- Basic knowledge of the pediatric population and pharmacotherapy required to provide safe, quality pharmaceutical care for children
  - Core competencies have been suggested by pediatric pharmacy organizations (Boucher, 2015)

Dosing Considerations

- Determining the appropriate dose of a medication requires an assessment of the patient's **age, weight, height, disease state and clinical status**
- Most medications require weight-based dosing, using the patient's actual body weight in kilograms (kg)
  - Body Surface Area (BSA) (m^2) = $\sqrt{}$(height [cm] x weight [kg]/3,600)
  - Age (e.g. montelukast) or weight (e.g. oseltamivir) categories
- Drug information can be limited due to the lack of double-blind, randomized, controlled trials for dosing
  - Results from less rigorous studies are used for dosing information

Assessment of **Age**

Abbreviation	Age Range
Neonate	Birth to 28 days of life
Infant	1 month (28 days) to 12 months of age
Child	1 to 11 years of age
Adolescent	12 to 18 years of age
Adult	>18 years of age

- **FDA:** pediatrics = birth to 16 years of age
  - Infants = 1 month to 2 years of age
  - Children = 2 to 12 years of age
  - Adolescents = 12 to 16 years of age
- **AAP:** pediatrics = birth to 21 years of age

Assessment of **Weight**

- Ideal Body Weight (IBW)
  - IBW (kg) = (height^2 [cm] x 1.65)/1,000
- Adjusted Body Weight (ABW)
  - May be used in adolescent population, similar to adults
- Dosing adjustments based on IBW or ABW are primarily based on adult data
  - Use in pediatric population is exploratory, as formulas do not take into account pharmacokinetic differences in children compared to adults
- Use weight-based dosing for patients <18 years of age and <40 kg (Matson, 2017)
  - For children >40 kgs, weight-based dosing should be used until the patient's dose or dose per day exceeds that recommended for adults

Assessment of Growth (**Height / Weight**)

- Growth Charts
  - World Health Organization (WHO): birth to 2 years of age
  - Centers for Disease Control and Prevention (CDC): 2 to 20 years of age
- Assess: head circumference, height/length, weight, body mass index (BMI)
  - Underweight: BMI <5th percentile
  - Healthy weight: BMI 5th to <85th percentile
  - Overweight: BMI 85th to <95th percentile
  - Obese: BMI ≥ 95th percentile
- Medication dosing errors occur in a higher rate in overweight and obese children (Miller, 2010)

Common Dosing Errors

- mg/kg/**dose** vs. mg/kg/**day**
  - Caution with how doses are listed in references
    - mg/kg every **X** hours
    - mg/kg/day divided every **X** hours
    - mg/kg/day divided **X** times per day
- Combination products
  - Dose based off of active component (e.g. ampicillin in ampicillin/sulbactam)
- Maximum weight-based dose
  - Maximum dose in adults should not be exceeded when using weight-based dosing in pediatrics

Example: Piperacillin/tazobactam

200 to 300 mg **piperacillin**/kg/**day** divided every 6 to 8 hours

Assume: 300 mg/kg/day divided every 8 hours

- Child weighing **20 kg**
  - 20 kg x 300 mg/kg/day = 6000 mg/day
  - 2000 mg every 8 hours
  - Premix 2.25 g bag
    - 2000 mg piperacillin

OK

- Child weighing **22 kg**
  - 22 kg x 300 mg/kg/day = 6600 mg/day
  - 2250 mg every 8 hours
  - Premix 2.25 g bag
    - 2000 mg piperacillin

✕

Example: Piperacillin/tazobactam

200 to 300 mg **piperacillin**/kg/**day** divided every 6 to 8 hours

- Child weighing 50 kg
  - 50 kg x 200 to 300 mg/kg/day = 10,000 to 15,000 mg/day (***max 12,000 mg/day***)
  - 12,000 mg/day → 3,000 mg every 6 hours or 4,000 mg every 8 hours

- Dosage Forms
  - 3.375 g = Piperacillin 3 g and tazobactam 0.375 g
  - 4.5 g = Piperacillin 4 g and tazobactam 0.5 g

Dosage Form Considerations

Solid Dosage Forms

- Ability to swallow solid dosage forms (~age 7) (Zajicek, 2013)
- Some tablets can be crushed or capsules can be opened (ISMP, 2020)
- Dietary issues (e.g. carbohydrate content for child on ketogenic diet)
- Feeding tubes

Liquid Dosage Forms

- Provide most flexibility
- Preferred unit of measurement = milliliter (mL)
  - Avoid "teaspoon" or "tablespoon"
- Oral syringe with calibration marks
  - Dose rounding
- Volume consideration
  - Use most concentrated formulation

Assessment of **Vital Signs**

- Electronic Health Records often have reference ranges that may be set as adult values
- Respiratory rate and pulse are generally ***higher*** in children
  - Highly variable when a pediatric patient is in distress
- Blood pressure is generally ***lower*** in children
- Temperature is the same
  - Normal: 36.5 – 37.5℃
    - Neonates with sepsis – temperature may be higher or lower than normal
  - Rectal temperatures are most accurate in infants and children < 3 years of age

Assessment of **Renal Function**

Schwartz Equation	Bedside Schwartz Equation
(Height [cm] x k) / SCr (mg/dL)	**0.413 x (height [cm] / SCr [mg/dL])**
k = 0.33 for premature infants (<1yr)	
k = 0.45 for infants 1-52 weeks old	
k = 0.55 for children 1-13 years old	
k = 0.55 for adolescent females 13-18 years old	
k = 0.7 for adolescent males 13-18 years old	
SCr = serum creatinine	

- Schwartz Equation may overestimate renal function (Schwartz, 2009)
- Bedside Schwartz developed to improve upon Schwartz Equation and validated using "newer" methods to measure serum creatinine (isotope dilution mass spectrometry [IDMS] traceable)
  - Based off cohort of children with chronic kidney disease (CKD)
  - Only applied to patients 1-18 years of age
- Results are normalized to 1.73m^2 (reported as mL/min/1.73m^2)

Assessment of **Renal Function**

- Absolute change in serum creatinine and urine output must be considered
  - Goal urine output >0.5 – 1 mL/kg/hour
- Acute Kidney Injury (AKI) (KDIGO, 2012)
  - Increase in serum creatinine by ≥0.3 mg/dL from baseline within 48 hours
  - Increase in serum creatinine by ≥1.5 times baseline within the prior 7 days
  - Urine volume of ≤0.5 mL/kg/hour 6 hours

Therapeutic Drug Monitoring: **Vancomycin**

- 2020 Guidelines (Rybak, 2020)
  - Challenge: diversity in developmental pharmacology from neonates → adolescents
  - Revised primarily due to concerns of nephrotoxicity with the use of trough monitoring
  - Factors important in determine exposure: age, weight, renal function, MIC (Le, 2015)
  - Limited outcomes data
    - *Staphylococcus aureus* bacteremia
      - Trough >15 mg/L not associated with improved outcomes, but increased AKI (McNeil 2016, 2017)
      - AUC/MIC >400 not associated with improved outcomes (Hahn, 2015)
  - Dosing in children should be designed to achieve an AUC/MIC of 400 – 600 mg•h/L
    - Correlates to trough of 7 - 10 mg/L

Therapeutic Drug Monitoring: **Vancomycin**

- Empiric dosing: 60 – 80 mg/kg/day divided every 6 hours (MIC ≤ 1 mg/L)
  - Children 3 months to < 12 years of age: 80 mg/kg/day
  - Children ≥ 12 years of age: 60 – 70 mg/kg/day
- Unlikely to achieve target AUC exposure if MIC > 1 mg/L
- Renal impairment: 45 mg/kg/day divided every 8 hours (Le, 2014)
- Monitoring of both serum concentrations and renal function imperative

Therapeutic Drug Monitoring: **Vancomycin**

- Minimizing AKI risk
  - Function of vancomycin exposure
    - 2.7-fold increased risk of AKI when vancomycin trough concentration ≥ 15 mg/L (Fiorito, 2018)
    - 2.5-fold increased risk of AKI when vancomycin AUC of ≥ 800 mg•h/L and trough concentrations of ≥ 15 mg/L (Le, 2015)
  - Avoid doses >100 mg/kg/day

- Therapeutic drug monitoring – AUC
  - 1 concentration (trough) → Bayesian estimation
  - 2 concentration (peak and trough) → First-order PK equations

Equations

Elimination rate: $Ke = \frac{Ln(\frac{Conc_1}{Conc_2})}{\Delta t(hr)}$

Half-life: $Thalf = \frac{Ln(2)}{ke}$

Extrapolated peak concentration: $Cmax = \frac{Conc_1}{e^{-Ke(t-tinf)}}$

Extrapolated trough concentration: $Cmin = Conc_2 \times e^{-Ke(\tau - t)}$

Volume of distribution: $Vd = \frac{Dose}{Ke \times Cmax \times tinf} \times \frac{1-e^{(-Ke \times tinf)}}{1-e^{(-Ke \times \tau)}}$

Area under the curve 24 hours: $AUC = \frac{Daily\ dose}{Ke \times Vd}$

New Dose = $Ke \times Vd \times AUC_{target}$

EMERGING CONCERNS WITH
ACID SUPPRESSIVE THERAPY

Acid Suppressive Therapy (AST)

Acid suppressive therapy

- Histamine H_2-receptor antagonists (H_2RAs)
- Proton pump inhibitors (PPIs)

Indications

- Dyspepsia
- Eosinophilic esophagitis
- Erosive esophagitis
- Gastric and duodenal ulcers
- Gastroesophageal reflux disease (GERD)
- *Helicobacter pylori* gastritis
- Hypersecretory conditions (e.g. Zollinger-Ellison syndrome)
- Prophylaxis

Increasing Use of AST in Children

- Increasing PPI usage
  - **Quadrupled** from 1999 → 2003 (Barron, 2007)
  - **Doubled** from 2004 → 2008 (Illueca, 2014)
- Why?
  - Overtreatment of physiologic reflux (newborns)
  - Prolonged treatment durations

GER vs. GERD

- Gastroesophageal Reflux (GER)
  - Movement of stomach contents into the esophagus and sometimes though mouth/nose
  - "Happy spitters"
  - Mild feeding problems (e.g. occasional prolonged feeds or interrupted feeds)
  - Normal
    - Begins at 2-3 weeks
    - Peaks between 4-5 months
    - Resolves at 9-12 months
- Gastroesophageal Reflux **Disease** (GER**D**)
  - Refusal to feed
  - Crying and/or arching the back during feeds
  - Blood or greenish color in spit-up
  - Increase in frequency or intensity of spit-up
  - Stomach is distended / hard
  - Respiratory symptoms (e.g. wheezing, coughing)
  - Not gaining weight appropriately
  - Fewer wet diapers / bowel movements

Negative Effects of AST

- PPIs do not relieve symptoms related to GER in infants
- Growing body of research revealing negative effects of PPI therapy

Adults

- Chronic kidney disease
- Decreased bone mass
- Fractures
- Gastric cancers, infections, polyps
- Mortality

Children

- *Clostridium difficile* infections
- Community/hospital acquired pneumonia
- Obesity
- Asthma
- Fractures

AST and **Fracture** Risk in Children

(Wagner, 2019)

- AST during first year of life may be associated with an increased fracture rate during the first 5 years of life

	0-5 Years	0-1 Years	2-5 Years
Caffeine	0.79 (0.40 – 1.58)	1.60 (0.39 – 6.63)	0.72 (0.34 – 1.53)
PPIs	1.43 (1.13 – 1.81)	1.14 (0.60 – 2.15)	1.47 (1.14 – 1.89)
Postnatal corticosteroids	1.15 (0.82 – 1.60)	0.87 (0.40 – 1.91)	1.17 (0.81 – 1.69)
Diuretics	1.40 (0.75 – 2.61)	1.28 (0.32 – 5.10)	1.42 (0.71 – 2.82)
H_2RA	1.07 (0.95 – 1.20)	1.34 (0.95 – 1.89)	1.05 (0.93 – 1.18)

AST and **Fracture** Risk in Children

(Malchodi, 2019)

	Unadjusted HR (95% CI)	Adjust HR (95% CI)
★ Male sex	1.08 (1.07 – 1.10)	1.08 (1.06 – 1.09)
Preterm birth	0.98 (0.95 – 1.02)	1.01 (0.97 – 1.05)
LBW	0.90 (0.86 – 0.95)	0.90 (0.85 – 0.94)
★ Previous fracture	1.85 (1.75 – 1.96)	3.59 (3.22 – 4.00)
Anti-epileptic medication	0.98 (0.92 – 1.04)	0.99 (0.93 – 1.05)
Overweight / obesity	1.12 (1.09 – 1.14)	0.99 (0.95 – 1.04)
★ PPI	1.23 (1.15 – 1.32)	1.23 (1.14 – 1.31)
H_2RA	1.13 (1.10 – 1.15)	1.04 (0.99 – 1.09)
★ Both	1.32 (1.26 – 1.38)	1.31 (1.25 – 1.37)

AST and **Fracture** Risk in Children

(Malchodi, 2019)

Fracture hazard ↑ with *duration* of AST exposure for PPI H_2RA Both

7,998 (9%) PPI	
Days on Medication	**Adjusted HR (95% CI)**
0 – 30 days	1.19 (1.11 – 1.29)
30 – 60 days	1.20 (1.09 – 1.33)
60 – 150 days	1.23 (1.13 – 1.33)
>150 days	1.41 (1.32 – 1.52)

71,578 (73%) H_2RA	
Days on Medication	**Adjusted HR (95% CI)**
0 – 30 days	1.14 (1.09 – 1.18)
30 – 60 days	0.99 (0.90 – 1.08)
60 – 120 days	1.16 (1.11 – 1.21)
>120 days	1.22 (1.17 – 1.27)

17,710 (18%) Both	
Days on Medication	**Adjusted HR (95% CI)**
0 – 120 days	1.17 (1.06– 1.29)
120 – 192 days	1.31 (1.18 – 1.47)
192 – 338 days	1.20 (1.08 – 1.32)
>338 days	1.50 (1.37 – 1.65)

AST and **Fracture** Risk in Children

(Malchodi, 2019)

Fracture hazard ↑ with *earlier initiation* for PPI Both

	First 6 months (n=84,845)	6-12 months (n=12,441)	12-24 months (n=8,390)
Male sex	1.08 (1.06 – 1.09)	1.08 (1.06 – 1.09)	1.08 (1.07 – 1.10)
Preterm birth	0.99 (0.96 – 1.04)	1.03 (0.98 – 1.07)	1.02 (0.97 – 1.06)
LBW	0.90 (0.85 – 0.95)	0.89 (0.84 – 0.94)	0.89 (0.84 – 0.94)
Previous fracture	3.57 (3.20 – 3.98)	3.52 (3.14 – 3.95)	3.50 (3.13 – 3.93)
Anti-epileptic medication	0.98 (0.92 – 1.05)	0.98 (0.92 – 1.05)	0.98 (0.92 – 1.05)
Overweight / obesity	0.99 (0.94 – 1.04)	0.99 (0.94 – 1.05)	0.99 (0.94 – 1.04)
PPI	1.23 (1.14 – 1.33)	1.21 (1.05 – 1.39)	1.06 (0.91 – 1.24)
H2RA	1.04 (0.99 – 1.10)	1.04 (0.92 – 1.17)	0.91 (0.75 – 1.11)
Both	1.32 (1.26 – 1.38)	1.23 (1.07 – 1.41)	1.38 (1.16 – 1.65)

AST and **Asthma** Risk in Children

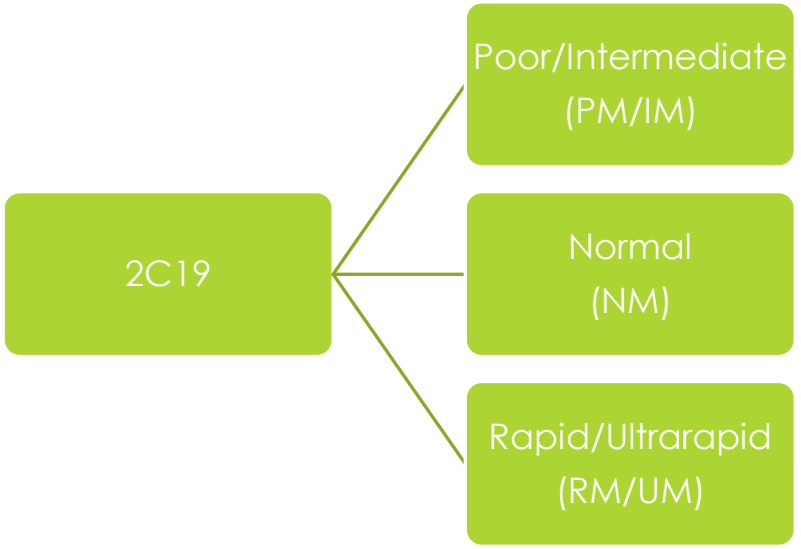
(Wang, 2021)

Variable	PPI Initiators, Incidence rate (n=80,870)	Non-initiators, Incidence Rate (n=80,870)	Hazard Ratio (95% CI)
Primary	21.8	14.0	1.57 (1.49 – 1.64)
Age group			
<6 months	153.4	83.0	1.83 (1.65 – 2.03)
6 months to <2 years	113.8	58.2	1.91 (1.65 - 2.22)
2 years to <6 years	24.1	17.4	1.38 (1.09 - 1.74)
6 years to <12 years	17.5	11.5	1.53 (1.37 – 1.72)
≥12 years	14.6	9.8	1.49 (1.39 – 1.59)
Timing of asthma onset			
≤ 90 days	29.5	18.2	1.62 (1.42 – 1.85)
91 – 180	29.3	16.9	1.73 (1.52 – 1.98)
≥181	20.0	13.1	1.53 (1.45 – 1.62)

a. Incidence rate calculated as events per 1,000 person-years

PPI and 2C19 Phenotype

- CYP2C19 inactivates PPIs
- Common genetic variants give rise to several metabolizer phenotypes (slow → rapid)
- Differences in CYP2C19 activity may have clinical significance (Bernal, 2019)



PPI and 2C19 Phenotype

(Bernal, 2019)

	PM/IM (n=183)	NM (n=267)	RM/UM (n=220)	PM/IM vs. NM	NM vs. RM/UM
Total infections	1 (0-3)	2 (0-3)	1 (0-3)	0.10	0.03
Respiratory infections	1 (0-2)	1 (0-3)	1 (0-2)	0.17	0.07
Gastrointestinal infections	0 (0-1)	0 (0-1)	0 (0-1)	0.4	0.1

PM/IM = poor metabolizer/intermediate metabolizer
NM = normal metabolizer
RM/UM = rapid metabolizer/ultrarapid metabolizer

Infection events reported as median (interquartile range)

- CYP2C19 metabolizer status was a significant risk factor for infection events
  - Odds Ratio 0.70 [95% CI 0.50 – 0.97] for RM/UM vs. NMs

Antimicrobial Stewardship

DURATION OF TREATMENT

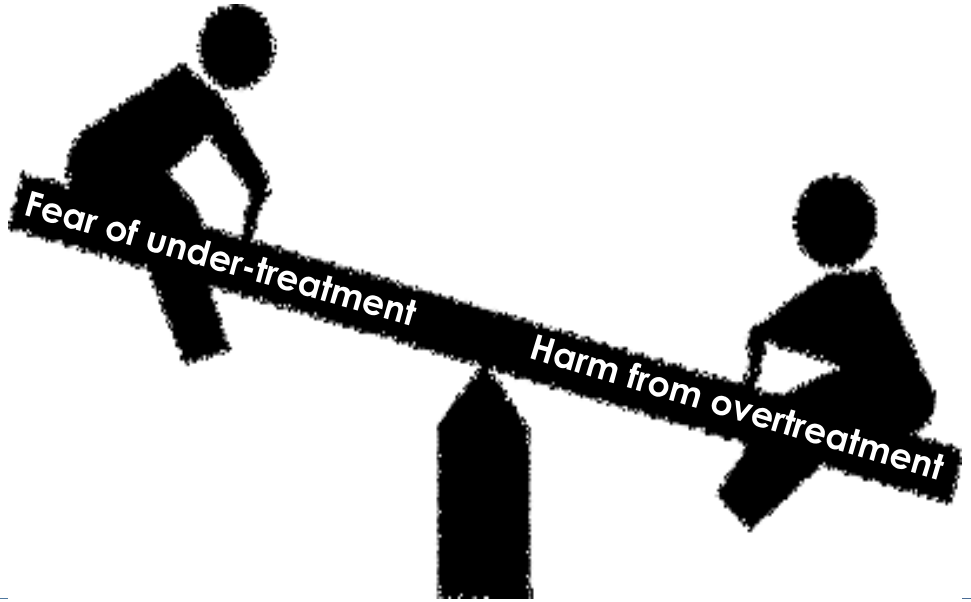
Antimicrobial Resistance

- **Target** vs. **Collateral** (Llewelyn, 2017)
  - **Target**: Mutations conferring antibiotic resistance arise spontaneously and selected for during treatment
    - Causes: multifactorial, **duration**
    - Examples: MDR Pseudomonas, tuberculosis, HIV
  - **Collateral**: commensal organisms in gut, skin or mucous membranes develop antimicrobial resistance during treatment of other infections
    - Causes: broad-spectrum antibiotic use, **duration**
    - Examples: *S. aureus*, *Enterobacteriaceae*

https://www.cdc.gov/antibiotic-use/community/about/antibiotic-resistance-faqs.html

Data Lacking in Children

- Adults: shorter durations OK for infections such as pneumonia, urinary tract infections, sinusitis, cellulitis (Royer, 2018; Hanretty, 2018)



Discharge Antibiotic Stewardship

- The 4 D's of Discharge Stewardship (Hersch, 2016)
  - Diagnosis
  - Drug
  - **Duration**
  - Designated clinician

Acute Otitis Media (AOM)

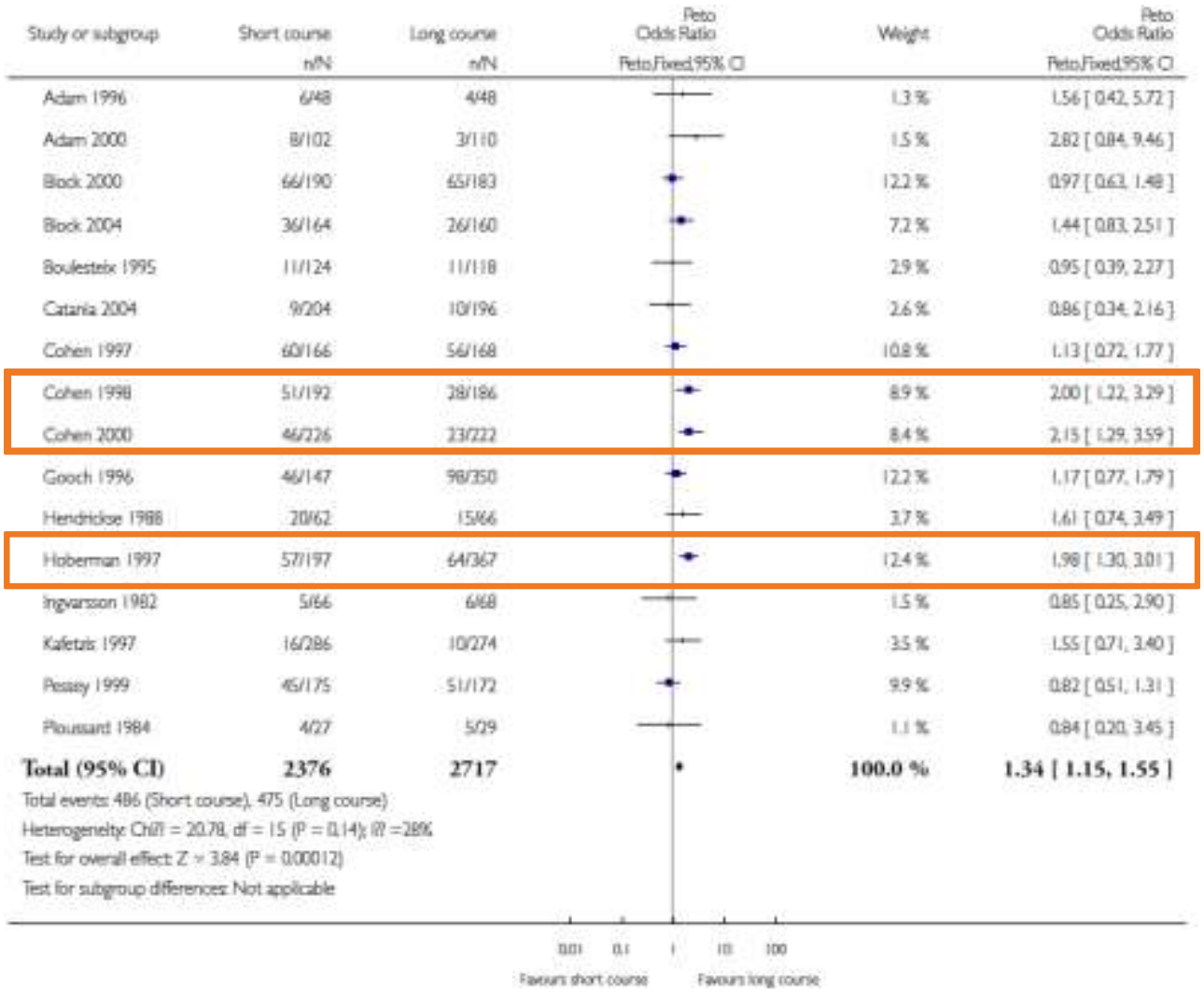
- Affects children > adults
- Commonly caused by bacteria and viruses
- Middle ear inflammation, fluid accumulation resulting and infection
- ¾ children will have a pediatrician sick visit for AOM by 3 years of age

AOM Duration of Treatment

- Duration (Lieberthal, 2013)
  - **10 days**
    - severe or < 2 years old
  - **7 days**
    - 2 – 5 years of age with mild-moderate symptoms
  - **5 – 7 days**
    - ≥ 6 years of age with mild-moderate symptoms

Duration of Therapy

The optimal duration of therapy for patients with AOM is uncertain; the usual 10-day course of therapy was derived from the duration of treatment of streptococcal pharyngotonsillitis.



(Kozyrskyj, 2010)

Shortened Antimicrobial Treatment for Acute Otitis Media in Young Children

(Hoberman, 2016)

Table 2. Clinical-Failure Rates for the Index Episode of Acute Otitis Media at or before the End-of-Treatment Visit, According to Selected Characteristics at Entry.*

Characteristic	10-Day Group (N=257)	5-Day Group (N=258)	All Children (N=515)	Odds Ratio (95% CI)†	P Value
	no. of children with clinical failure/total no. (%)				
All children	39/238 (16)	77/229 (34)	116/467 (25)	NA	—
Age at entry					0.94
12–23 mo	15/116 (13)	41/111 (37)	56/227 (25)	Reference	
6–11 mo	24/122 (20)	36/118 (31)	60/240 (25)	1.0 (0.7–1.6)	

- 520 children
- Amox/Clav 90 mg/kg/day
- Primary outcome: clinical response (treatment failure) at ~14 days
  - 16% (10D) vs. 34% (5D); difference = 17% points; 95% CI = 9 – 25
  - Non-inferiority criteria not met
- Colonization with penicillin non-susceptible pathogens: 44% (5D) vs. 47% (10D) (p=0.58)

Eradication Rate

(Arguedas, 2006)

TABLE 2. Bacteriologic Response at the On Therapy Visit (Day 4 to 6) Among Bacteriologically Evaluable Children

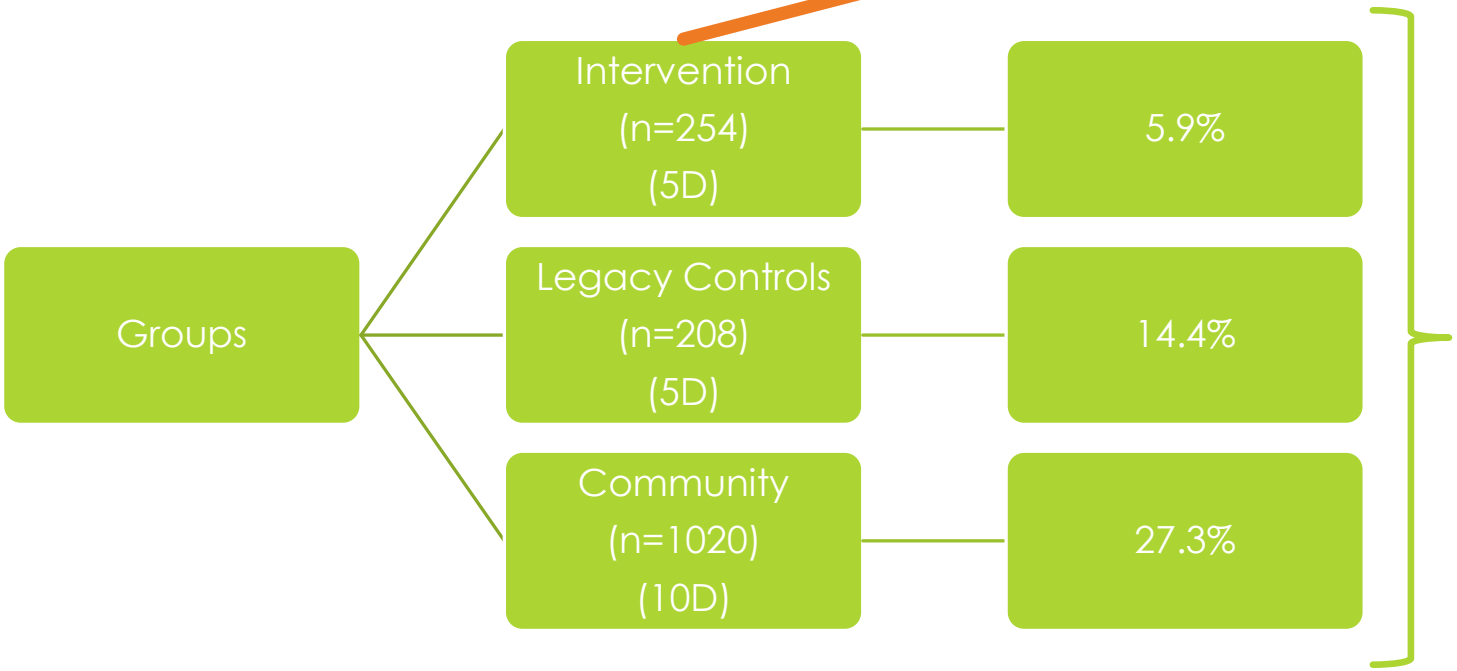
	Eradication Rate		95% CI for Difference
	Age ≤24 mo	Age >24 mo	
Bacteriologic response by child	119/171 (70)*	51/59 (86)	−28.0, −5.7
Target pathogen eradication rate			
Overall	144/200 (72)	57/66 (86)	−24.7, −4.0
Haemophilus influenzae†	67/97 (69)	23/28 (82)	−30.0, 3.8
ß-Lactamase-positive	15/17 (88)	3/3 (100)	−27.1, 3.6
ß-Lactamase-negative	50/76 (66)	17/22 (77)	−32.0, 9.0
Streptococcus pneumoniae†	59/83 (71)	22/26 (85)	−30.5, 3.4
Penicillin-susceptible	33/36 (92)	17/19 (89)	−14.3, 18.7
Penicillin-intermediate	16/23 (70)	2/4 (50)	−32.9, 72.0
Penicillin-resistant	8/21 (38)	2/2 (100)	−82.7, −41.1
Moraxella catarrhalis	15/17 (88)	6/6 (100)	−27.1, 3.6
ß-Lactamase-positive	14/16 (88)	3/3 (100)	−28.7, 3.7
ß-Lactamase-negative	—	—	
Streptococcus pyogenes	3/3 (100)	6/6 (100)	—

*Numbers in parentheses, percent.
†Includes isolates that constituted single pathogen and mixed infections.

Tympanocentesis

(Pichichero, 2013)

10% of subjects had antibiotic change due to non-susceptible pathogen



Otitis Prone

3 episodes in 6 months

4 episodes in 12 months

AOM Summary

- Duration (Lieberthal, 2013)
  - **10 days**
    - severe or < 2 years old
  - **7 days**
    - 2 – 5 years of age with mild-moderate symptoms
  - **5 – 7 days**
    - ≥ 6 years of age with mild-moderate symptoms

Urinary Tract Infections (UTI)

- UTI occurs when pathogenic organisms infect any of the structural components of the urinary tract
- Incidence in pre-pubertal children
  - Females = 3%
  - Males = 1%
- In children < 12 months who present with fever, UTI prevalence is higher
- Duration: 7 to 14 days (Roberts, 2011)

8. The optimal duration of antimicrobial treatment has not been determined. RCTs of head-to-head comparisons of various duration would be valuable, enabling clinicians to limit antimicrobial exposure to what is needed to eradicate the offending uropathogen.

Lower UTI
(Michael, 2010)

- Positive culture at the end of treatment
  - Short (2-4 days) vs. Standard (7-14 day)
  - Lower UTI (afebrile) – excluded children with upper UTI (e.g., pyelonephritis)

Timeframe	No. of Studies	Short Duration	Standard Duration	RR [95% CI]
End of Treatment	8	34/232 (15.9%)	27/191 (14.1%)	1.06 [0.64 – 1.76]
1 to 3 months	6	19/138 (13.8%)	20/131 (15.3%)	0.83 [0.46 – 1.47]
3 to 15 months	4	42/129 (32.6%)	35/109 (32.1%)	1.05 [0.73 – 1.52]
1 to 15 months	10	62/267 (23.2%)	57/240 (23.8%)	0.95 [0.70 – 1.29]

Upper UTI
(Strohmeier, 2014)

- Pyelonephritis
  - Oral only (10-14 days) vs. IV (3 days) + Oral (10 days)

Outcome	No. of Studies	Oral Only	IV + Oral	RR [95% CI]
Persistent UTI at 72 hours	2	1/266 (0.4%)	1/276 (0.4%)	1.10 [0.07 – 17.41]
Kidney damage	4	88/470 (19%)	106/473 (22%)	0.82 [0.59 – 1.12]

SCOUT Study

(Zaoutis, 2021)

- Short (5 days) vs. Standard (10 days)
  - Non-inferiority study
- Children 2 – 10 years of age
  - Stratified by presence or absence of fever
- 693 children → 345 (short) vs. 348 (standard)
  - Median age: 4 (IQR 2-6) years
  - 96% female

SCOUT Study

(Zaoutis, 2021)

- Treatment success: 322/336 (95%) short vs. 326/328 (99%) standard
  - Treatment failure was not related to age group, fever at presentation, antibiotic type, or study site.
  - No significant differences between groups the in the rates of adverse events, recurrent infection, clinical symptoms that may have been related to UTI, or emergent antibiotic resistance.
- Both 5 and 10 day treatment durations resulted in high success rates
  - Non-inferiority criteria not met
  - Could not conclude 5 days was not inferior to 10 days

UTI Summary

European Society of Pediatric Urology (Radmayr, 2020)

UTI Type	Total Duration (Days)
Uncomplicated UTI	4 – 7
Pyelonephritis in neonate	14 – 21
Pyelonephritis infants aged 1-6 months	10 – 14
Uncomplicated pyelonephritis infants > 6 months old	7 – 10
Complicated pyelonephritis/urosepsis at any age	10 – 14

Community Acquired Pneumonia (CAP)

- One of the most common, serious infections in childhood
- 1 million outpatient antibiotic courses annually
- 70% of children will be infected with a virus (EPIC study)
- Duration: 10 days (Bradley, 2011)
  - Complicated (e.g., parapneumonic effusions/empyema): 2-4 weeks

Non-Severe CAP

(Haider, 2008)

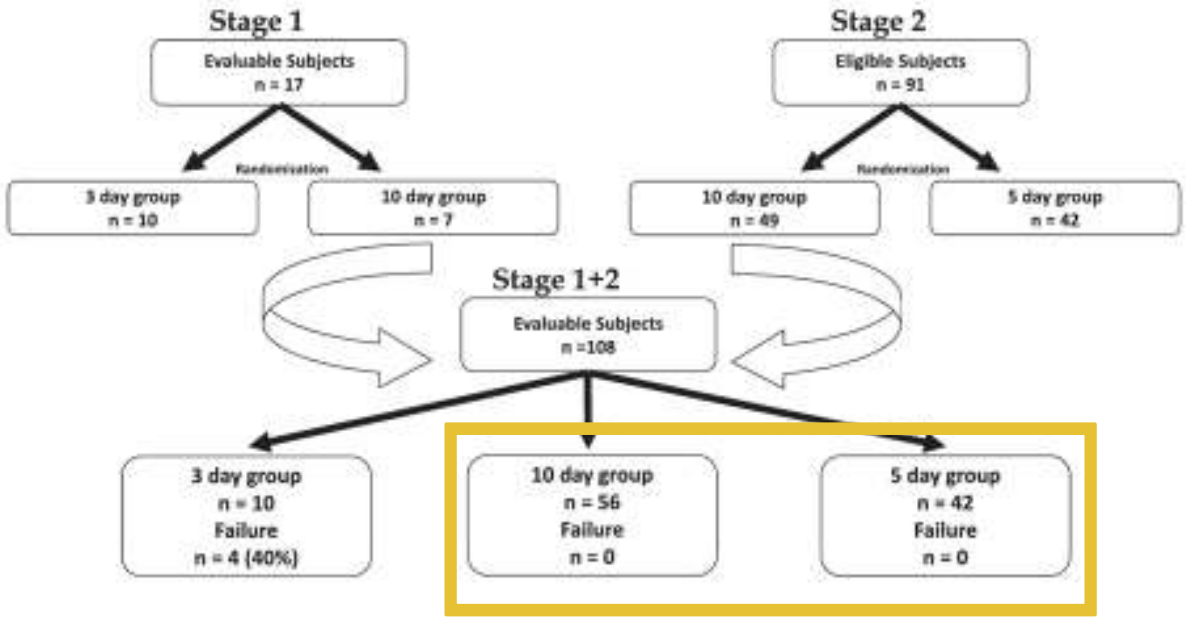
- Children 2 to 59 months

Outcome	No. of Studies	3 days	5 days	RR [95% CI]
Clinical cure	2	1783/2013 (89%)	1794/1999 (90%)	0.99 [0.97 – 1.01]
Treatment failure	3	310/2892 (11%)	287/2871 (10%)	1.07 [0.92 – 1.25]
Relapse	4	110/2735 (4%)	100/2734 (4%)	1.09 [0.84 – 1.42]

- Studies performed in developing countries
- CAP diagnosed by World Health Organization (WHO) criteria
  - Clinical findings + respiratory rate thresholds (i.e., no radiographic evidence)
- Many children probably had viral pneumonia

Radiographically Confirmed CAP
(Greenberg, 2014)

- Mean age ~ 2 years
- Stage 2: 5 days vs. 10 days of amoxicillin
- Primary outcome: treatment failure
- 5 days was not inferior to 10 days



SAFER Study
(Pernica, 2021)

- Short (5 days) vs. Standard (10 days)
  - Non-inferiority trial
- Children 6 months to 10 years of age
  - Pneumonia with positive chest radiograph
  - Treated in emergency department
    - Excluded if hospitalized
- 281 children → 140 (short) vs. 141 (standard)
  - Median age: 2.6 (IQR 1.6 – 4.9) years

10 days Amoxicillin	
5 days Amoxicillin	5 days Placebo

SAFER Study
(Pernica, 2021)

- Clinical cure at 14-21 days
  - Per-protocol: 101/114 (88.6%) short vs. 99/109 (90.8%) standard
    - Non-inferiority criteria not met
  - Intention-to-treat: 108/126 (85.7%) short vs. 106/126 (84.1%) standard
    - Non-inferior
- Both 5 and 10 day treatment durations resulted in high success rates
  - Non-inferiority criteria not met (for per-protocol analysis)
  - Could not conclude 5 days was not inferior to 10 days

SAFER Study
(Pernica, 2021)

- Clinical failure criteria
  - No more than 1 fever from day 4 through follow-up (14-21 days)
  - No additional antibacterial because of persistent/progressive symptoms

- Post-hoc analysis: ***clinical cure not requiring additional intervention***
  - 107/112 (95.5%) short vs. 104/109 (95.4%) standard
    - Noninferior (but, could not formally conclude based on a priori, per protocol analysis)

- 5 days of antibiotics likely works as well as 10 days for most children with CAP

CAP Summary

- Short Course vs Standard Course Outpatient Therapy of Community Acquired Pneumonia in Children (SCOUT-CAP) [NCT02891915]
  - Multi-center, randomized, double-blind, placebo-controlled, superiority
  - Short (5-day) vs. standard (10-day) course in children (6 months – 6 years) who are diagnosed with CAP
- Uncomplicated: 10 days is most likely too long

Take Home Points

- Medication dosing in the pediatric population is individualized and based on patient-specific factors such as age, weight or body surface area
- Questions and challenges exist when applying pharmacokinetic goals derived from adults to the general pediatric population (e.g., vancomycin)
- Acid suppressive therapy has several negative adverse effects in children and should be limited to the shortest duration possible
- Duration of antibiotic therapy is an important component of antimicrobial stewardship and further studies are needed to clarify the optimal duration for common pediatric infectious diseases