Pediatrics PRN Focus Session—Staying Ahead of the Curve: Contemporary Dosing Strategies in Infectious Disease
Activity No. 0217-0000-11-082-L01-P (Application-Based Activity)

Monday, October 17
3:45 p.m.–5:45 p.m.
Convention Center: Rooms 317 & 318

Moderator: Katherine P. Smith, Pharm.D., BCPS
Associate Professor of Pharmacy Practice, Director of Continuing Education, University of Southern Nevada College of Pharmacy, South Jordan, Utah

Agenda

3:45 p.m.  Pushing the Limits: Aggressive Infectious Disease Strategies in Pediatric Patients
Holly D. Maples, Pharm.D.
Associate Professor, Department of Pharmacy Practice; Director, Pediatric Pharmacy Practice and Infectious Disease Residency Programs, University of Arkansas for Medical Sciences; College of Pharmacy Codirector, Antimicrobial Stewardship Program, Arkansas Children’s Hospital, Little Rock, Arkansas

4:45 p.m.  Following the Curve: Pharmacokinetic-Guided Dosing of Antimicrobials in Pediatrics
Jennifer Le, Pharm.D., BCPS (AQ Infectious Diseases)
Associate Professor of Clinical Pharmacy, University of California, San Diego Skaggs School of Pharmacy and Pharmaceutical Sciences La Jolla, California

Faculty Conflict of Interest Disclosures
Jennifer Le: received grant funding from Cubist, Pfizer, Astellas, and National Institutes of Health; speaker's bureau Pfizer
Holly D. Maples: no conflicts to disclose.

Learning Objectives

1. Identify specific infections/situations where aggressive dosing should be considered.
2. Provide a rationale based on the literature for maximizing doses in pediatric patients with infections.
3. Compare antibiotic treatment durations with expected outcomes in common pediatric infections.
4. Identify the need for re-vaccination in pediatric patients with immunocompromised conditions.
5. Apply pediatric-specific pharmacokinetic data on antifungal agents to patients with serious fungal infections.
6. Describe unique pharmacokinetic parameters that require dosing alterations in pediatric patients.
7. Identify and implement appropriate measurement and monitoring strategies (Pk, AUC/MIC, etc) for antimicrobials in infected pediatric patients.
Self-Assessment Questions

Self-assessment questions are available online at www.accp.com/am
Staying Ahead of the Curve: Contemporary Dosing Strategies in Pediatric Infectious Disease

Holly D. Maples, Pharm.D.
Associate Professor, Department of Pharmacy Practice; Director, Pediatric Pharmacy Practice and Infectious Disease Residency Programs, University of Arkansas for Medical Sciences; College of Pharmacy; Co-Director, Antimicrobial Stewardship Program, Arkansas Children’s Hospital, Little Rock, Arkansas

10/17/2011

Conflicts of Interest
No conflicts to disclose.

Objectives
- Identify specific infections/situations where aggressive dosing should be considered
- Provide rationale based on the literature for maximizing doses in pediatric patients with infections
- Compare antibiotic treatment durations with expected outcomes in common pediatric infections
- Identify the need for re-vaccination in pediatric patients with immunocompromised conditions

Case 1
- RJ is a 5 year old boy who presents to the ED with fever of 38.5°C and the complaint that it “really” hurts to walk on his left leg.
- PMHx: not significant
- Labs:
  - ESR >73 mm/hr
  - CRP >270 mg/L

Osteomyelitis: Etiology
- **Staphylococcus aureus**
  - 90% of confirmed cases
- **Streptococcus pyogenes**
- **Streptococcus pneumoniae**
- **Kingella kingae**
  - Under age 3

**Osteomyelitis: Changing Epidemiology**
- **The MRSA Epidemic**
  - Has altered antibiotic regimens required to treat
  - Has impacted the severity of illness
    - Serum inflammatory markers
    - Higher and more prolonged fever
    - Greater lengths of hospital stay
  - Compared to MSSA or culture negative osteo
  - Other complications
    - DVT, multifocal infection, adjacent pyomyositis, progression to chronic osteo


**Osteomyelitis: Diagnosis**
- **Serum Markers**
  - ESR
  - CRP
  - WBC

- **Culture**
  - Blood cultures + in 50%
  - More common with PVL

- **Imaging**
  - MRI
  - Repeat MRI

- **PCR**
  - Kingella
  - MRSA

**Osteomyelitis: Empiric Treatment**
- **Vancomycin**
  - Bactericidal
  - Susceptible, but increasing MICs

- **Clindamycin**
  - Bacteriastic
  - Increasing rates of resistance
    - (2010:IP is 80%, OP is 86% non-CF)

**Osteomyelitis: Vancomycin**
- **Desired Concentrations**
  - Trough 15-20 ug/mL
  - Why?

- **Pediatric Initial Dosing**
  - 15 mg/kg/dose every 6 hours
  - Is this enough?

**Osteomyelitis: Second-Line**
- **Linezolid**
  - 10 mg/kg/dose every 8 hours

- **Daptomycin**
  - 1st line in adults
  - Pediatric Dosing?
    - 6 mg/kg/day
    - 10 mg/kg/day

- **Trimethoprim/sulfamethoxazole plus rifampin**

**Osteomyelitis: Vancomycin**
- **Role of Initial “Bolus” Dose of Vancomycin**
  - Adult Guidelines
  - 25 -30 mg/kg (actual body weight)
    - Give over 2 hours
    - Utilize antihistamine prior

- **Role of Vancomycin Bolus in Kids?**

Liu C et al. CID 2011;52:e10-05.


Liu C et al. CID 2011;52:e10-05.
Osteomyelitis: Synergy

- Rifampin and/or Gentamicin
- No clinical data available to support addition of rifampin in typical cases of osteomyelitis.


Osteomyelitis: Novel Pipeline Options

- Fifth Generation Cephalosporins
  - Ceftaroline
  - Ceftobiprole
  - Not currently approved for osteomyelitis
  - Pediatric PK studies underway
  - Jacqueline et al.
    - Studied efficacy of ceftaroline in an experimental rabbit model and compared to vancomycin and linezolid.


Osteomyelitis: Early Step Down Therapy

- Efficacy
  - 4 to 6 weeks IV vs early transition to oral

- Complications
  - Catheter related complication
  - Readmission


Osteomyelitis: Duration of Therapy

- IDSA Guidelines
  - 4-6 weeks

- Peltola et al.
  - 20 day antibiotic course was not inferior to 30 days
  - 89% of infections in this study were caused by MSSA

- Williams et al.
  - Culture negative acute osteoarticular infections were mild compared to culture confirmed MRSA
  - However, culture negative infections had a duration of treatment triple.


Case 2

- SJ is a 13 year old admitted to the PICU post ATV vs. tree accident. Skull fracture with CSF leak and ventilated x 10 days. Now has chest x-ray that is indicative of pneumonia. Tmax 39.2
- BAL culture: GNR’s

CDC Public Health Image Library

Empiric coverage: Vancomycin and Piperacillin/tazobactam

VAP: Etiology

- HA pneumonia
  - MRSA
  - Streptococcus pneumonia
  - SPACE bugs
    - Serratia
    - Pseudomonas
    - Acinetobacter
    - Citrobacter
    - Enterobacter
- Increased risk for MDR

Bradley J. CID 2010;51:S136-43.
**VAP: Etiology**

- **Early-Onset**
  - Within first 4 days of hospitalization
  - Antibiotic sensitive bacteria

- **Late-Onset**
  - ≥ 5 days after hospitalization
  - MDR pathogens

**VAP: Empiric Treatment**

- **Monotherapy vs. Double Coverage**
  - Cefepime, ceftazidime
  - Antipseudomonal Penicillin
  - Beta-lactam/beta-lactamase inhibitor
  - Monoabactam
  - Antipseudomonal fluoroquinolone
  - Aminoglycoside

- **Early vs Late Onset**
  - Cefepime, ceftazidime
  - Antipseudomonal Penicillin
  - Beta-lactam/beta-lactamase inhibitor
  - Monoabactam
  - Antipseudomonal fluoroquinolone
  - Aminoglycoside

**VAP: Culture Results**

<table>
<thead>
<tr>
<th>Organism Name</th>
<th>Antimicrobial</th>
<th>MICs &amp; SYs</th>
<th>Initial</th>
<th>Final</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter</td>
<td>Colistin, Rifampin</td>
<td>&lt;0.5, 32</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td>Colistin</td>
<td>&gt;0.5, 16</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>Aminoglycoside</td>
<td>&gt;2, 1</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>Carbapenem, aminoglycoside, fluoroquinolone, or β-lactam</td>
<td>&gt;0.5, 16</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**VAP: MDR Acinetobacter Treatment**

- **in vitro**
  - Colistin & rifampin
  - Colistin + Imipenem
  - Rifampin
  - Imipenem & rifampin
  - Rifampin & ampicillin-sulbactam

- **Clinical**
  - Cefepime and amikacin
  - Rifampin + Colistin
  - Colistin + 1 or more of the following:
    - Carbapenem, aminoglycoside, fluoroquinolone, or β-lactam

**VAP: Role of MCBT**

- Multiple combination bactericidal test
- What is it?
  - Allows clinician to choose combinations of antibiotics that together have in vitro bactericidal activity against MDRQ.
  - Burkholderia cepacia
  - Stenotrophomonas maltophilia
  - Pseudomonas aeruginosa
  - Acinetobacter baumannii
- Does not guide and predict successful antibiotic therapy
  - 
  - CF - most studied (Pseudomonas, B. cepacia)
  - Acinetobacter

**VAP: Role of Aerosolized Antibiotics**

- Aerosolized antimicrobial agents can achieve 200-fold greater concentrations in respiratory secretions than levels achieved in the blood

- Inhaled alone vs. combination with systemic?
  - Czosnowski et al.
  - Ghannam et al.
  - Lu et al.
Respiratory Zones

- Inhaled antibiotics achieve high concentrations in the conductive zone and very little in the respiratory zone.
- IV or oral antibiotics achieve low concentrations in the sputum, but high concentrations in the respiratory tissue.

Respiratory Zones

Conducting Zone
- Trachea
- Bronchi
- Bronchioles
- Terminal Bronchioles

Transitional & Respiratory Zones
- Respiratory bronchioles
- Alveolar ducts
- Alveolar sacs

VAP: Role of Biofilms

- MRSA
- Pseudomonas

Mucoid and Nonmucoid Pseudomonas in CF

<table>
<thead>
<tr>
<th>Property</th>
<th>Mucoid phenotype</th>
<th>Nonmucoid phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location in the lungs</td>
<td>Respiratory and conductive zone in sputum</td>
<td>Conductive zone in sputum</td>
</tr>
<tr>
<td>Biofilm formation in vitro</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Biofilm formation in vivo</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Multiple abs resistance due to conventional mechanisms</td>
<td>Seldom</td>
<td>Frequent</td>
</tr>
<tr>
<td>Resistance due to biofilm properties</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Responsible for lung tissue damage</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Induces pronounced antibody response</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Antibiotic Respiratory Formulations

- Inhalation antibiotics
  - TOBI
  - Amikacin
  - Colistin
  - Levofloxacin
  - Aztreonam

VAP: Treatment Options for Biofilm Respiratory Infections

- Colistin and Tobramycin inhaled?
- Fluoroquinolones and colistin?
- Role of inhaled aztreonam?
**VAP: Aminoglycoside Dosing Goals**

- Depend on site of infection and MIC
  - Easy to reach
    - Peak Goal: 5-6 x MIC
  - Hard to reach
    - Peak Goal: 10-12 x MIC
- Traditional dosing (2.5 mg/kg/dose q8hr)
  - Goal Peak of 6-12 with Trough <2
- Once daily dosing
  - Synergy dosing
  - Renal insufficiency (traditional goals)


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**VAP: Aminoglycoside Dosing Goals**

- Extended interval dosing
  - Usually once daily, but with different goals
    - Example: Peak of 30 ug/mL
  - Goal Peak usually 8-10 times MIC (dependent on site of infection) with a 4-6 hour non-detectable level
  - PAE (post antibiotic effect)

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**VAP: Length of Therapy**

- Intravenous
  - 7-14 days
- Inhaled
  - 7-14 days from published studies used
  - No conclusive information


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**Case 3**

SJ is an 16 yo male with sexually acquired HIV diagnosed at age 14 who was initiated on antiretroviral therapy 18 months ago when his HIV viral load was >100,000 copies/ml and CD4 total was 115. He now has a non-detectable viral load and CD4 count of 455. You are the pharmacist who needs to evaluate SJ's immunization needs. What does he need?

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**Immunizations:**

**Immune Deficiency**

- Primary
  - B-lymphocyte
  - T-lymphocyte
  - Complement
  - Phagocytic function
- Secondary
  - HIV
  - Malignant neoplasm
  - Transplant
  - Splectomy
  - Immunosuppression/antimetabolite/radiation therapy

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**Immunizations**

Recommended Immunization Schedule for Persons Aged 7 Through 18 Years—United States—2011

Red Book online

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Staying Ahead of the Curve: Contemporary Dosing Strategies in Infectious Disease
**Immunizations: Adolescents**

- 69% of adolescents were Tdap
- 32% completed three-dose series in 2010, up from 27% in 2009

**Immunizations: HIV**

- Live Vaccines
  - Varicella
  - MMR

**Pneumococcal**
- 13 valent pneumococcal conjugate vaccine (PCV13)
- Pneumococcal polysaccharide (PPSV)

**Meningococcal**
- MCV4
- MPSV4

**Immunizations: HIV**

- Hepatitis A
  - 2 doses 6 months apart
- Hepatitis B
  - Serological testing recommended
  - Booster vaccination if their anti-HBs levels decrease below 10 mIU/mL

- HPV
- Hib
- Td
- Zoster
- Influenza

CDC. NIS-Teen Surveys, 2006-2010.

L’Huillier AG et al. HIV Medicine 2011; epub ahead of print

Questions
Following the Curve: Pharmacokinetic Guided-Dosing of Antimicrobials in Pediatrics

Jennifer Le, Pharm.D., BCPS-ID, FCCP
David L. Lawrence Convention Center in Pittsburgh, Pennsylvania
October 17, 2011

Objectives
- Apply pediatric-specific pharmacokinetic data on antifungal agents to patients with serious fungal infections.
- Describe unique pharmacokinetic parameters that require dosing alterations in pediatric patients.
- Identify appropriate measurement and monitoring strategies (i.e., AUC:MIC) for antimicrobials in infected pediatric patients.

Pharmacotherapy in Infectious Diseases

Pediatric Patient
- Immature humoral and cellular immunity
  - Active antibody production is not fully developed until 4 - 5 years old
- Age-specific physiological variability
  - Lack of matured renal function
  - Lack of matured hepatic function
  - Total body water content
  - Gastric pH
  - Gastric and intestinal motility
  - Albumin / protein binding
  - Less predictable drug exposure-response relationship
  - Unexpected responses
- Drug effects in adults are NOT similar in children

Conflict of Interest

Jennifer Le, PharmD, BCPS-ID
Associate Professor of Clinical Pharmacy
University of California, San Diego
Skaggs School of Pharmacy and Pharmaceutical Sciences
Email: jenle@ucsd.edu
Website: http://pharmacy.ucsd.edu/faculty/le.shtml

Current: NIH/NIAID 5K23AI089978
Previous: Investigator-initiated Research Grants from Cubist, Pfizer and Astellas; Speaker’s Bureau for Pfizer

Pediatric Patient
- Pharmacokinetic differences between adults and neonates/children
- Pharmacokinetic differences within pediatric age groups
  - Preemies
  - Neonates
  - Infants
  - Children
  - Adolescents

Staying Ahead of the Curve: Contemporary Dosing Strategies in Infectious Disease


Bug

- Minimum inhibitory concentration (MIC)
  - Dependent on bug and drug
  - Not well correlated to clinical outcomes for antifungal agents
- Resistance
- Site of infection and drug exposure

Drug

- PHARMACOKINETICS
  - Concentration vs. Time
- PHARMACODYNAMICS
  - Concentration vs. Effect
- PK/PD
  - Effect vs. Time

Pharmacodynamics

Linking Drug and Bug to Patient

Drug: PK Parameters
- Measure of exposure
- Time, Peak, AUC

Bug: MIC
- Good indicator of drug potency
- Nothing about time course activity

Drug: PK-PD Index for Exposure and Effect

<table>
<thead>
<tr>
<th>Index</th>
<th>% T&gt;MIC</th>
<th>AUC/MIC</th>
<th>Peak/MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>% of time above the MIC over 24 h</td>
<td>Area under the concentration-time curve over 24 h at steady-state divided by MIC</td>
<td>Peak level divided by MIC</td>
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<tr>
<td>Drugs</td>
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<tr>
<td>Penicillins</td>
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<td>Cephalosporins</td>
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<td>Carbapenems</td>
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<td>Monobactams</td>
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<td>Metronidazole</td>
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<td>Daptomycin</td>
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<td>Ketolides</td>
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<td>Macrolides</td>
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<td>Azithromycin</td>
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<td>Sterptagramins</td>
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<td>Glycopeptides</td>
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<td>Vancomycin</td>
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<td>Tetracyclines</td>
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<td>Azoles</td>
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<tr>
<td>Oxazolidinones</td>
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<td>Aminoglycosides</td>
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<tr>
<td>Fluoroquinolones</td>
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</table>

Monte Carlo Simulation (MCS)

- Powerful pharmacological tool used to associate drug exposure to an outcome, including clinical efficacy or adverse event.
- Integrates existing knowledge
- Predict the best drug dose
  Probability of target attainment (PTA)

- Beta-lactams
- Vancomycin
- Voriconazole
- Posaconazole
- Fluconazole
Prolonged Infusion of Beta-Lactams

- MCS in 2- and 12-year-old of various beta-lactams against *Pseudomonas aeruginosa*
- Prolonged infusion of 3-hr markedly improved PTA
  - Cefepime: 79 to 100%
  - Ceftazidime: 80 to 100%
  - Imipenem/cilastatin: 41 to 91%
  - Meropenem: 33 to 97%

---

Prolonged Infusion of Beta-Lactams

<table>
<thead>
<tr>
<th>Bacterial Organism</th>
<th>Comparison</th>
<th>Time Above MIC</th>
<th>AUC/MIC</th>
<th>Death Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. difficile</em></td>
<td>79 to 100%</td>
<td>&gt;30%</td>
<td>600</td>
<td>90%</td>
</tr>
<tr>
<td><em>C. difficile</em></td>
<td>80 to 100%</td>
<td>&gt;30%</td>
<td>600</td>
<td>90%</td>
</tr>
<tr>
<td><em>C. difficile</em></td>
<td>41 to 91%</td>
<td>&gt;30%</td>
<td>600</td>
<td>90%</td>
</tr>
<tr>
<td><em>C. difficile</em></td>
<td>33 to 97%</td>
<td>&gt;30%</td>
<td>600</td>
<td>90%</td>
</tr>
</tbody>
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Vancomycin

- Vancomycin serum troughs ≥15 mcg/mL in children is associated with a 3-fold increase in nephrotoxicity by multivariable logistic regression.

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Vancomycin

- Multi-centered cohort study of hospitalized pediatric patients between 3 months to 21 years of age admitted to Miller Children’s Hospital and Rady Children’s Hospital
- Population-based pharmacokinetic (PPK) analysis was performed using a non-linear mixed effects modeling software, NONMEM 7.2.1 (Icon, Dublin, Ireland) to determine volume of distribution and clearance.
- Empiric Bayesian post-hoc individual parameters with Monte Carlo simulation (MCS, with N=4094) was used to compare target attainment of AUC/MIC ≥ 400 mg-hr/L and trough ≥ 15 mcg/mL (assuming MIC of 1 mcg/mL).
Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 707</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR1), years</td>
<td>6.6 (2.2 – 13.4)</td>
</tr>
<tr>
<td>&lt; 1, no. (%)</td>
<td>85 (12)</td>
</tr>
<tr>
<td>1 to &lt; 2, no. (%)</td>
<td>71 (10)</td>
</tr>
<tr>
<td>2 to &lt;12, no. (%)</td>
<td>332 (47)</td>
</tr>
<tr>
<td>≥12, no. (%)</td>
<td>219 (31)</td>
</tr>
<tr>
<td>Median weight (IQR1), kg</td>
<td>22.7 (12.5 – 46.6)</td>
</tr>
<tr>
<td>Male gender, no. (%)</td>
<td>374 (53)</td>
</tr>
<tr>
<td>Intensive care unit stay, no. (%)</td>
<td>267 (38)</td>
</tr>
<tr>
<td>Concurrent use of nephrotoxic agents, no. (%)</td>
<td>270 (38)</td>
</tr>
<tr>
<td>Mean baseline serum creatinine (SCr) ± SD (IQR1), mg/dL</td>
<td>0.48 ± 0.33 (0.3-0.6)</td>
</tr>
<tr>
<td>SCr ≥ 0.9, no. (%)</td>
<td>57 (8)</td>
</tr>
<tr>
<td>Mean empiric vancomycin dose ± SD (IQR1), mcg/kg/day</td>
<td>42 ± 13 (31 - 50)</td>
</tr>
<tr>
<td>Every 6 hr, no. (%)</td>
<td>296 (37)</td>
</tr>
<tr>
<td>Every 8 hr, no. (%)</td>
<td>380 (51)</td>
</tr>
</tbody>
</table>

Vancomycin MCS

<table>
<thead>
<tr>
<th>Dosing Regimen</th>
<th>Mean ± SD</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 mg/kg/day</td>
<td>Peak, mcg/mL</td>
<td>24 ± 8</td>
</tr>
<tr>
<td></td>
<td>Trough, mcg/mL</td>
<td>11 ± 8</td>
</tr>
<tr>
<td></td>
<td>AUC, mg-hr/L</td>
<td>398 ± 102</td>
</tr>
<tr>
<td>45 mg/kg/day</td>
<td>Peak, mcg/mL</td>
<td>31 ± 10</td>
</tr>
<tr>
<td></td>
<td>Trough, mcg/mL</td>
<td>10 ± 8</td>
</tr>
<tr>
<td></td>
<td>AUC, mg-hr/L</td>
<td>447 ± 216</td>
</tr>
<tr>
<td>60 mg/kg/day</td>
<td>Peak, mcg/mL</td>
<td>36 ± 12</td>
</tr>
<tr>
<td></td>
<td>Trough, mcg/mL</td>
<td>16 ± 11</td>
</tr>
<tr>
<td></td>
<td>AUC, mg-hr/L</td>
<td>596 ± 289</td>
</tr>
<tr>
<td>70 mg/kg/day</td>
<td>Peak, mcg/mL</td>
<td>42 ± 15</td>
</tr>
<tr>
<td></td>
<td>Trough, mcg/mL</td>
<td>19 ± 13</td>
</tr>
<tr>
<td></td>
<td>AUC, mg-hr/L</td>
<td>696 ± 337</td>
</tr>
</tbody>
</table>

Correlation AUC and Trough

60 mg/kg/day

Vancomycin PD Target: AUC vs Trough

1 N=4,094; assumes MIC of 1 mcg/mL
All patients who achieved target Cmin also achieved target AUC

Voriconazole PK: Adults

- Non-linear Michaelis-Menten; 3 - 5 mg/kg/dose every 12 hours
- Loading dose of 8 mg/kg for high Cmax that exceeds MIC values for fungal pathogens

Voriconazole PK: Children

- Linear kinetics at 3 - 4 mg/kg/dose every 12 hrs
- Non-linear kinetics at 4 - 8 mg/kg/dose every 12 hrs
- AUC is 3-fold lower in children receiving 4 mg/kg q12h than in adults
- Conclusion: Higher doses required in children to achieve drug exposures consistent with those in adults.
Prospective study of 52 adults with invasive fungal infections

Efficacy
- Two-fold increase in blood level is associated with success [OR 1.8; 95% CI, 1.1–3.1; p<0.03]
- 70% probability of response at troughs > 1 mcg/mL

Neurological Toxicity
- 31% encephalopathy with troughs > 5.5 mcg/mL
- None with troughs < 5.5 mcg/mL
- Statistically significant at p<0.002

Therapeutic Range: 1 to 5.5 mcg/mL
- Higher trough > 2 mcg/mL

Retrospective study of 40 children with 108 trough levels
- Troughs < 1 mcg/mL ➔ 2.6-fold increased odds of all-cause mortality (95% CI, 1.6 - 4.8; p<0.002)
- Median sampling time 9.0 hr (1.3 - 36)
- Serum concentrations were not associated with hepatotoxicity
- Neurotoxicity was not assessed

Conclusion: Pharmacodynamic association between a voriconazole trough > 1.0 mcg/mL and survival

46 subjects age 0.8 to 20.5 yrs
- 7 mg/kg/dose every 12 hr produced troughs
  - Median 1.287; 95% CI 0.176 to 3.4
- An increase of 1 mg/kg in dose will increase serum levels by ~0.52 mcg/mL
- Oral 200-mg fixed dose twice daily results in suboptimal levels
  - 48% of 35 trough levels obtained from 21 pediatric patients age 7-18 years were < 1 mcg/mL

Open-label, multicenter study of 48 immuno-compromised pediatric patients 2 to 11 years old (n=24 in cohort 2)
- 7 mg/kg every 12 h in children provides AUC comparable to 4 mg/kg every 12 h in adults
- Wide variability in AUC in children receiving 7 mg/kg every 12 h

Comparison of 12 pediatrics 2 to 11 years old and 12 adults
- 7 mg/kg every 12 h in children provides trough levels comparable to 4 mg/kg every 12 h in adults
- 56% of children had troughs < 1 mcg/mL or > 6 mcg/mL, indicating wide intra- and inter-subject variability

7 mg/kg every 12 h in children provides AUC comparable to 4 mg/kg every 12 h in adults
- Wide variability in AUC in children receiving 7 mg/kg every 12 h

Michael et al. Voriconazole Pharmacokinetics and Safety in Immunocompromised Children Compared to Adult Patients. AAC 2010;54:3225-3232

7 mg/kg every 12 h in children provides AUC comparable to 4 mg/kg every 12 h in adults
- Wide variability in AUC in children receiving 7 mg/kg every 12 h

Walsh et al. Pharmacokinetics, safety, and tolerability of voriconazole in immunocompromised children. AAC 2010 ;54:4116-23

Voriconazole PD

- Target AUC 40,000 ng-hr/mL

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>6 mg/kg IV</th>
<th>8 mg/kg IV</th>
<th>6 mg/kg PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 to &lt;6</td>
<td>18,216</td>
<td>25,566</td>
<td>6,959</td>
</tr>
<tr>
<td>6 to &lt;12</td>
<td>16,234</td>
<td>34,681</td>
<td>10,076</td>
</tr>
<tr>
<td>All patients</td>
<td>17,249</td>
<td>29,776</td>
<td>8,373</td>
</tr>
</tbody>
</table>

- Doses of 4 mg/kg in adults and 8 mg/kg in children are needed to achieve similar AUC
- Trend towards higher AUC in older kids
- Decreased clearance

Voriconazole Interactions

- Consider dose adjustment of following agents:
  - Methadone
  - Statins
  - Calcium channel blockers
  - Benzodiazepines
  - Vinca alkaloids
  - Sulfonamides
  - Warfarin
  - Oral contraceptives
  - Others
- Increase dose of voriconazole:
  - Phenytoin
- Contraindications:
  - Quinidine
  - Rifampin
  - Rifabutin
  - Carbamazepine
  - Long-acting barbiturates
  - Albendazole
  - Erythromycin
  - Erythromycin base
  - Erythromycin ethylsuccinate
  - Ertapenem
  - Flucytosine
  - Phenytoin
  - Ethosuximide
  - Valproic acid
  - Warfarin
  - St. John’s Wort

Voriconazole Metabolism

- P450 Enzymes
  - CYP3A4
  - CYP2C19
  - Flavin-containing monooxygenase 3 (FMO3)

Voriconazole Safety

- Visual Disturbances
  - Abnormal vision, color vision change, photophobia are common with serum levels > 6 mcg/mL
  - Self-limiting and reversible
- Hepatotoxicity
  - Risk of ↑LFTs increases by 7 to 17% for every 1 mcg/mL increase in random drug level
  - No association to concentrations in pediatric studies
  - Case report of severe liver dysfunction due to unusually high voriconazole levels
Voriconazole Safety

- Central and peripheral neurological toxicities
  - Trough levels 3-5 x the normal median values
  - 4 patients experienced encephalopathy in prospective study
- Drug level > 5.5 mcg/mL
  - Concomitant use of omeprazole and voriconazole
  - Side effects resolved within 1-3 days after drug discontinuation
- Signs of encephalopathy should prompt blood level measurements with drug discontinuation or dose reduction.

Voriconazole Dosing

- Children ≥ 12 years old and Adults
  - Loading: 6 mg/kg/dose every 12 hrs x 2 doses
  - Maintenance: 4 mg/kg/dose every 12 hr
- Children ages 2-11 years old
  - Loading dose NOT required
  - 5 - 7 mg/kg/dose every 12 hr (IDSA)
  - 8 mg/kg/dose every 12 hr (Walsh)

Patient Case One

- A 7 yo boy with a history of AML who failed induction therapy received umbilical cord transplantation (UCBT). On day 60 s/p UCBT, he developed GVHD that was treated with corticosteroid plus tacrolimus. The patient develops febrile neutropenia with respiratory symptoms.
- Diagnostics, Labs and Cultures
  - Chest CT: (+) two peripheral nodules
  - Galectomanann (GM) test performed → 0.80
  - awaiting results, liposomal amphoB started
  - Results from BAL revealed A. fumigatus

- What intravenous voriconazole dose?
  - IDSA Guideline 5-7 mg/kg/dose every 12 hr
  - New data suggests 8 mg/kg/dose every 12 hr

Patient Case One

- After 3 days of IV voriconazole, patient’s clinical status remains unchanged.
- What course of action do you recommend?
  - Monitor voriconazole serum trough obtained right before the next dose after 3 to 7 days of therapy
  - Four days after voriconazole trough was obtained (day #7 of voriconazole 7 mg/kg every 12 hr), the result was reported at 0.6 mcg/mL.

- What is your next course of action?

Patient Case One

- Target trough levels:
  - > 1 mcg/mL for efficacy
  - < 5 to 6 mcg/mL for safety
- Data from primary literature suggests:
  - Dose increase by 1 mg/kg → serum concentration increase by ~0.52 mcg/mL
- Action: Increase patient’s voriconazole dose to 8 mg/kg/dose (~ 1 mg/kg/dose increase) every 12 hr
- Subsequent patient’s trough level was 1.1 mcg/mL

Posaconazole Absorption

- Oral suspension formulation
  - High-fat meal enhances absorption by 3- to 4-fold
  - Gastric pH
    - Omeprazole, low pH beverages, and (metoclopramide)
    - Gastric mucosal alteration and reduced food intake from mucositis
  - Posaconazole levels reduced ~50% in allogeneic BMT recipients
- New tablet and capsule formulations unaffected by food under investigation in adults.
**Fluconazole in Neonates**

- **Treatment of invasive candidiasis**
  - **Loading dose:** 25 mg/kg achieved target more rapidly
  - **Maintenance:** 12 mg/kg/day
    - **AUC of 440 mcg/mL (or AUC/MIC>50 with MIC<8 mcg/mL)**
  - Preterm infants achieve a higher median AUC (682 mcg*hr/L).

**Therapeutic concentration in neonates with invasive candidiasis requires dosing greater than recommended in reference texts.**

**Fluconazole in Neonates**

- **Early prevention of candidiasis**
  - 3 or 6 mg/kg twice weekly for first 42 days of life
  - **AUC of 50 or 100 mg*hr/L**
  - **Concentrations ≥ 2 or 4 mcg/mL**
  - (or 3 mg/kg every 2 – 3 days for 2 to 6 weeks)

- **Late prevention of candidiasis**
  - 6 mg/kg dose every 72 hours – 3 mg/kg daily
  - Serum creatinine ≥ 1.3 mg/dL have delayed clearance
  - Dose adjustment if not improve within 96 hours

**Posaconazole in Kids**

- 61 pediatric patients
  - Doses: 100 mg twice to 300 mg four times daily
  - 100 serum levels from 30 patients
  - Lower levels
    - 5-yr age increase – 0.4 ng/mL increase
    - SCID
    - Black/other race
    - Achieving target concentrations is challenging
    - TDM should be used to verify adequate absorption and medication adherence.

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**Posaconazole PD**

- Treatment of refractory invasive aspergillosis
  - Posaconazole 800 mg per day in 67 adults
    - ≥ 1.25 mcg/mL had highest clinical response (70%)
- Prophylaxis
  - 17% of 85 adult patients developed fungal infections
    - Levels < 500 mcg/mL (median ~290)
    - Multivariable regression showed reduced exposure
  - Drugs - proton pump inhibitor, metoclopramide, phenytoin, rifampin
  - Disease - mucositis, diarrhea, early post-transplant period in SCT recipients

**Fluconazole in Neonates**

- **Indication for Drug Monitoring**
  - Hypersensitivity or contraindications
  - 4- or 5-finger width
  - Lack of response
  - Drug-drug interaction

- **Time of 1st level targets**
  - 375 - 850 mcg/mL

- **Target serum concentrations**
  - Trough >0.5 mcg/mL
  - Trough >1-2 mcg/mL
  - Trough >0.5 mcg/mL
  - AUC of 50 or 100 mg*hr/L

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