PATIENT CASE

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- Would you…?
  - A) Initiate 30 mg/kg/day divided q8h
  - B) Initiate 45 mg/kg/day divided q8h
  - C) Initiate 70 mg/kg/day divided q6h
  - D) Initiate 60 mg/kg/day divided q6h
  - E) Initiate linezolid, as vancomycin is unsafe in pediatric patients
PATIENT CASE

- What goal trough would you target?:
  - A) 15-20 mcg/mL
  - B) 10-15 mcg/mL
  - C) 10-20 mcg/mL
  - D) 7-10 mcg/mL

OBJECTIVES

- 1. Describe the pharmacokinetics and monitoring of vancomycin
- 2. Assess the efficacy of current vancomycin dosing and monitoring strategies.
- 3. Identify incidence and risk factors for vancomycin-associated nephrotoxicity in the pediatric population.
OBJECTIVE 1: PHARMACOKINETICS

VANCOMYCIN

http://faculty.ccbcmd.edu/~gkaiser/SoftChalk%20BIOL%20230/Bacteria%20Genetics/chemical_control/antibiotics/antibiotics_print.html
VANCOMYCIN PHARMACOKINETICS

- 1\textsuperscript{st} order
- Protein-bound
- Vd = 0.5-0.9 L/kg
- T1/2 ~6h

VANCOMYCIN ADME

- Absorption:
  - 100\% IV
- Distribution:
  - Widely distributed
- Metabolism:
  - None apparent
- Excretion:
  - 90\% renal
**VANCOMYCIN ADME**

- In pediatrics:
  - Renal Clearance

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>1-2</th>
<th>3-4</th>
<th>5-9</th>
<th>10-11</th>
<th>12-13</th>
<th>14-15</th>
<th>16+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scr (mg/dL)</td>
<td>0.1-0.4</td>
<td>0.1-0.5</td>
<td>0.2-0.6</td>
<td>0.3-0.7</td>
<td>0.4-0.8</td>
<td>0.5-0.9</td>
<td>0.8-1.3</td>
</tr>
</tbody>
</table>

- Total body water changes with growth
- Vd changes with growth

---

**PEDIATRIC PATIENTS**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Definition</th>
<th>Vd (L/kg)</th>
<th>Clearance (ml/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
<td>1st month of life, regardless of gestational age</td>
<td>0.57 – 0.69</td>
<td>1 (0.63 – 1.5)</td>
</tr>
<tr>
<td>Infants</td>
<td>1 month to 2 years</td>
<td>0.26 – 1.05</td>
<td>1.2 (0.33 – 1.87)</td>
</tr>
<tr>
<td>Children</td>
<td>&gt;2 years to &lt;13 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adolescents</td>
<td>13 years to 17 years</td>
<td>0.5 – 0.9</td>
<td>1 (0.71 – 1.31)</td>
</tr>
<tr>
<td>Adults</td>
<td>18 years or greater</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
VANCOMYCIN MICS

- MIC: broth microdilution

![Broth dilution method for measuring minimum inhibitory concentration of antibiotics](http://aws.labome.com/figure/te-127-5.png)

VANCOMYCIN MICS

- Etest

- VITEK (2)

VANCOMYCIN

- Invasive gram positive infections

- Spectrum:

<table>
<thead>
<tr>
<th>Gram – Positive</th>
<th>Anaerobes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus sp. (Group A,B,C,G)</td>
<td>Actinomyces</td>
</tr>
<tr>
<td>Step. Pneumoniae</td>
<td>C. Difficile</td>
</tr>
<tr>
<td>E. Faecalis</td>
<td>Clostridium sp.</td>
</tr>
<tr>
<td>Staph. Aureus (MSSA, MRSA)</td>
<td>Peptostreptococcus sp.</td>
</tr>
<tr>
<td>S. epidermidis</td>
<td></td>
</tr>
</tbody>
</table>

SANFORD GUIDE, 2014

VANCOMYCIN HISTORY

- 1956: Vancomycin Derived
- 1958: FDA Approved
- 1961: MRSA first reported
- 1970s: MRSA incidence increases
VANCOMYCIN HISTORY

1981 Moellering nomogram

Pharmacodynamics of Vancomycin and Other Antimicrobials in Patients with Staphylococcus Aureus Lower Respiratory Tract Infections

VANCOMYCIN

- 108 patients with lower respiratory tract infection

Outcomes:
- Time to bacterial eradication
- Time to clinical improvement

Moise-Broder et al. Clinical Pharmacokinetics, 2004
VANCOMYCIN

- AUC/MIC ≥ 400 correlated to troughs of 10-15
- ADULT data

Moise-Broder et al. Clinical Pharmacokinetics, 2004

VANCOMYCIN

Children ≠ Little Adults
OBJECTIVE 2: DOSING AND MONITORING

BACKGROUND

<table>
<thead>
<tr>
<th>Red Book</th>
<th>Sanford Fargo</th>
<th>IDSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 - 60 mg/kg/day Q 6 - 8 hours</td>
<td>30 - 60 mg/kg/day Q 6 - 8 hours</td>
<td>60 mg/kg/day Q 6 hours</td>
</tr>
</tbody>
</table>

“Data are limited to guide vancomycin dosing in children. IV vancomycin 15 mg/kg/dose every 6 hours is recommended in children with invasive disease” (B-III) - IDSA
BACKGROUND

POP QUIZ!
How many pediatric vancomycin studies were included in IDSA guideline?

VANCOMYCIN DOSING INADEQUACY
- Frymoyer 2009
  - Only vancomycin dosing study cited
  - Conclusion: 60 mg/kg/day > 40 mg/kg/day

- Eiland 2011
- Nassar 2012
- DaSilva 2013 (Hem Onc)
- Madigan 2013
CURRENT RECOMMENDATIONS

► What dose will reliably reach AUC/MIC goals?

► What troughs correspond to adequate treatment?

► What are the outcomes?

Improved Vancomycin Dosing in Children Using Area-Under-the-Curve Exposure

PK-PD TRIAL: METHODS

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 m. to 12 y. of age</td>
<td>Neonates</td>
</tr>
<tr>
<td>Vancomycin therapy</td>
<td>Premature</td>
</tr>
<tr>
<td>&gt;48h of treatment</td>
<td>Neonatal Intensive Care Patients</td>
</tr>
<tr>
<td>9/1/11 to 7/30/2013</td>
<td>Hemodialysis</td>
</tr>
<tr>
<td>Trough at &lt;96h</td>
<td>Interfering meds</td>
</tr>
</tbody>
</table>

1631 screened
929 excluded
702 included

Population-based pharmacokinetics:
- Non-linear mixed effect modeling
- Monte Carlo Simulations

Lee et al, Pediatr Infect Dis J, 2013
PK-PD TRIAL: RESULTS

Mean Clearance (L/h) vs. Age Group (years)

Bars represent one standard deviation

PK-PD TRIAL: RESULTS

Probability of Target Attainment (%) vs. Vancomycin Dosing Regimen (mg/kg/day)

AUC/MI/Ca ≥ 400*
AUC/MI/Cb ≥ 400**
Cmin ≥ 15
PK-PD TRIAL: RESULTS

- AUC/MIC > 400 = Trough ~ 8 – 9 mcg/mL
- Troughs highly variable based on age, weight, interval, SCr
- Q8h dosing had lower troughs than Q6h dosing, but with similar AUC/MIC

PK-PD TRIAL: STRENGTHS

- Large
- Multiple models
- Real patients
- Modeling good fit with patient data
PK-PD TRIAL: WEAKNESSES

- Mean clearance differed between hospitals
- MIC distributions differed between hospitals
- E test used for MICs
- No outcomes

PK-PD TRIAL: CONCLUSIONS

- Author’s recommended dosing:

<table>
<thead>
<tr>
<th>Dosing Regimen</th>
<th>Age Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 mg/kg/day</td>
<td>3 months to &lt; 2 years old</td>
</tr>
<tr>
<td>70 mg/kg/day</td>
<td>≥2 years old, Scr &lt; 0.45**</td>
</tr>
<tr>
<td>60 mg/kg/day</td>
<td>≥2 years old, Scr ≥ 0.45</td>
</tr>
</tbody>
</table>

** Could also consider this dosing if 30% or more MRSA isolates have MIC ≥ 1.5
PK-PD TRIAL: CONCLUSIONS

- Agree with findings and dosing recommendations
- Largest pediatric PK study to date
- Best guidance so far

Desired Vancomycin Trough Serum Concentration for Treating Invasive Methicillin-resistant Staphylococcal Infection

TROUGH TRIAL: METHODS

- Pharmacokinetic modeling
  - Chang
  - Lamarre
  - Wrishko

- "Hypothetical" patients

- 15 mg/kg q6 hours

- Assumed MIC of 1

TROUGH TRIAL: RESULTS

![Graph showing probability of AUC/MIC > 400 vs. vancomycin trough concentration.](image)
TROUGH TRIAL: RESULTS

- Necessary troughs highly dependent upon MIC
- Q8h dosing had lower troughs than Q6h dosing, but with similar AUC/MIC

Frymoyer et al, Pediatr Infect Dis J, 2013

TROUGH TRIAL: STRENGTHS

- Multiple models used
- Modeled guideline-recommended dose
- Large “n”
TROUGH TRIAL: WEAKNESSES

- No real patients
- Did not account for infection site
- No outcomes

TROUGH TRIAL: CONCLUSION

- 15 – 20 mcg/mL unnecessarily high
- 7 – 10 mcg/mL predictive of AUC/MIC >400
- 60 mg/kg/day q6h is unnecessary
- “Hypothetical benefit”
- Cannot account for resistance

Frymoyer et al, Pediatr Infect Dis J, 2013
TROUGH TRIAL: REBUTTAL STUDY

- Validation study

- 15 subjects, 0 – 18 years old

<table>
<thead>
<tr>
<th>Trough</th>
<th>&lt;5 mcg/mL (n = 2)</th>
<th>8 – 10 mcg/mL (n = 9)</th>
<th>&gt;14.5 mcg/mL (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC/MIC</td>
<td>100% &lt; 400</td>
<td>67% &gt; 400</td>
<td>100% &gt; 400</td>
</tr>
</tbody>
</table>

Hahn et al, Pediatr Infect Dis J, 2013

TROUGH TRIAL: CONCLUSION

- Lower troughs may be acceptable in pediatric patients

- NO OUTCOMES

- Multiple facets to consider:
  - MIC of organism
  - Patient clearance
  - Dosing regimen
  - Site of infection (CNS)
  - Risk of nephrotoxicity
OBJECTIVE 3: NEPHROTOXICITY

VANCOMYCIN

- Toxicities
  - Infusion reaction ("Red Man")
  - Ototoxicity
  - Nephrotoxicity

- Estimated incidence in adults: 5-40%

- Estimated incidence in children: 0-20%
Incidence and Risk Factors Influencing the Development of Vancomycin Nephrotoxicity in Children


NEPHROTOXICITY

- Retrospective cohort study
- 167 children \( \geq \) 1 week old to 19 years old
- Vanco \( \geq \) 48hours
- Similar dosing guideline to Sanford
NEPHROTOXICITY

- 14% nephrotoxicity

- Association with nephrotoxicity:
  - Trough >15
  - Furosemide use
  - Intensive care unit

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>N</th>
<th>Incidence</th>
<th>Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knoderer, 2013</td>
<td>General, ICU</td>
<td>859</td>
<td>19.4%</td>
<td>ICU admission, initial trough &gt;15</td>
</tr>
<tr>
<td>Ragab, 2013</td>
<td>General, ICU</td>
<td>265</td>
<td>27.2%</td>
<td>ICU admission, aminoglycosides</td>
</tr>
<tr>
<td>Totapally, 2013</td>
<td>ICU only</td>
<td>391</td>
<td>17.2%</td>
<td>Nephrotoxic drugs, high BUN</td>
</tr>
<tr>
<td>Cies, 2013</td>
<td>ICU only</td>
<td>113</td>
<td>8.8% and 5.4%</td>
<td>Troughs &gt;15 NOT ASSOCIATED</td>
</tr>
<tr>
<td>Moffett, 2015</td>
<td>Cardiac ICU, Case control</td>
<td>418</td>
<td>7.2%</td>
<td>Critical illness, ECMO, nephrotoxic medications</td>
</tr>
</tbody>
</table>
NEPHROTOXICITY

- Conclusions:
  - Conflicting results
  - Critical illness
  - Concomitant nephrotoxic drugs?
  - Troughs?

BACK TO OUR CASE…
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CONCLUSIONS

- Highly variable pharmacokinetics
- Dosing considerations more complex than mg/kg
- AUC/MIC > mg/kg in children
- Nephrotoxicity not as severe/common as we may have thought
CONCLUSIONS

- Reasonable to adopt Le’s dosing:

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Lee et al, Pediatr Infect Dis J, 2013

CONCLUSIONS

- NO OUTCOMES DATA IN PEDIATRICS
- Requires much further study
- Potential for software tools to assist in monitoring
  - T.D.M.S. 2000, BestDose
  - Based on single trough
- Useful as guidance
CONCLUSIONS

VANCOMYCIN THERAPY IN PEDIATRIC PATIENTS: “LEVELING UP”

QUESTIONS?
Thank you!
Carlina Grindeland, PharmD, BCPS
REFERENCES