Dosing Anti-Infectives in the Obese Pediatric Patient

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Disclosures

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Objectives

• Review epidemiology and impact of obesity on infections in children
• Understand relevant physiological changes associated with obesity
• NOT look at a complex dosing table
• Become familiar with the state of the art
• Summarize strategies to guide dosing and advance the field
Definitions

- Age, sex-specific
- Uses CDC growth charts revised in 2000, based on data up to 1994

<table>
<thead>
<tr>
<th>Category</th>
<th>BMI%</th>
<th>BMI z-Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean</td>
<td>&lt;85</td>
<td>&lt;1.04</td>
</tr>
<tr>
<td>Overweight</td>
<td>85 to &lt;95</td>
<td>1.04 to 1.64</td>
</tr>
<tr>
<td>Obese</td>
<td>≥95</td>
<td>&gt;1.64</td>
</tr>
</tbody>
</table>
Burden of pediatric obesity

>380 Million

WHO, 2021
Burden of pediatric obesity

1975 → 2016

+800%
Shifting demographic

Gerhart et al, 2022
Clinical difference?
Infectious outcomes in obese children

• Osteomyelitis (Kyler et al, 2021)
  • ~ double risk of surgical procedures
  • 1 day longer hospitalization

• Post-surgical infections (Bechard et al, 2013)
  • +/- increased rate of infections

• Sepsis (Maley et al, 2017)
  • Increased organ dysfunction
  • 0.6 days longer hospitalization
  • Increased hospital charges
Sepsis outcomes

357,701 pediatric hospitalizations for infection
5,685 in obese children

Maley et al, 2017
Physiologic changes in pediatric obesity

- Cardiac output +10-20% (L/min)
- Organ volume +15%
- GFR +30%
- Hematocrit
- Protein binding
- Organ blood flow (ml/min/kg)

Adipose (kg) = f(age, wt, BMI, sex)

DME/Transporters

Gerhart et al, 2022
Effect of increased adipose on drug PK

Lipophilic drug = Increased Vd

Lipophilic drug = Variable CL
Lipophilicity and Vd

Bruno et al, 2020
### Myopia

<table>
<thead>
<tr>
<th>Dose</th>
<th>AUC</th>
<th>CL</th>
<th>Cmax</th>
<th>Cmin</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>50</td>
<td>2</td>
<td>5</td>
<td>0.45</td>
</tr>
<tr>
<td>100</td>
<td>20</td>
<td>5</td>
<td>10</td>
<td>0.00</td>
</tr>
<tr>
<td>100</td>
<td>20</td>
<td>5</td>
<td>5</td>
<td>0.01</td>
</tr>
<tr>
<td>100</td>
<td>20</td>
<td>5</td>
<td>2</td>
<td>0.18</td>
</tr>
</tbody>
</table>
Basic PK

- $AUC = \frac{dose}{CL}$
- $t_{1/2} = \frac{\log(2) \times V_d}{CL}$
\[ IBW = \frac{cm^2 \times 1.65}{1000} \]

\[ AjBW = IBW + 0.4 \times (TBW - IBW) \]

Hall, 2015
Ross et al, 2015
Natale et al, 2017
Srinivas, 2018
Kyler et al, 2019
Takahashi et al, 2020
Smit et al, 2021
State of the Art
PBPK

Adults
Ghobadi et al, 2011

Commentary
Neely et al, 2011

Children
Gerhart et al, 2022
Clindamycin PBPK

(TBW)
(900 mg)
(600 mg)
TMP/SMX PBPK

Efficacy

Toxicity

Gerhart et al, 2022
# DNR PK in obese pediatric patients: PBPK

<table>
<thead>
<tr>
<th>Real population*</th>
<th>PK-SIM host model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard</td>
</tr>
<tr>
<td>Lean (n=38)</td>
<td>1.02 (0.84 – 1.24)</td>
</tr>
<tr>
<td>Overweight (n=17)</td>
<td>1.53 (1.24 – 1.88)</td>
</tr>
</tbody>
</table>

Geometric mean ratio (GMR) of the simulated : observed AUCs and the 90% confidence interval (CI) of the GMR

*Thompson et al, 2014

Parkikh et al, ACoP, 2022
Enzyme activity in adipose tissue

<table>
<thead>
<tr>
<th></th>
<th>CBR1</th>
<th>AKR1C1</th>
<th>AKR1C2</th>
<th>AKR1C3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean</td>
<td>1.14 (0.77 – 1.51)</td>
<td>1.58 (1.33 – 1.83)</td>
<td>0.46 (0.32 – 0.60)</td>
<td>0.61 (0.34 – 0.88)</td>
</tr>
<tr>
<td>Obese</td>
<td>1.33 (1.25 – 1.41)</td>
<td>2.11 (1.87 – 2.35)</td>
<td>0.90 (0.66 – 1.14)</td>
<td>1.09 (0.97 – 1.21)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.37</td>
<td><strong>0.02</strong></td>
<td><strong>0.02</strong></td>
<td><strong>0.02</strong></td>
</tr>
</tbody>
</table>
Bayesian Control
Begin with a model
Use the model
The parametric approach

Population CL  Data  Individual CL

Bayesian Prior  Bayesian Posterior
MAP-Bayesian Parametric model

**Maximum a posteriori Bayesian probability**

One version of the patient
Shrinkage towards population mean with sparse sampling
No probability of future success vs. failure
Non-Normal Populations

Simulated population (■)
Non-parametric estimation of population values (○)
Size proportional to probability

The entire population is accurately and precisely described.

Neely et al, 2012
Non-Normal Populations

Simulated population (□)

Mean (+) and percentile distributions of parametric population parameter estimates

Nobody is at the mean!

Missed the outlier completely.
NP MM Approach
Multiple Models
Multiple Models

![Graph showing two lines representing Vorticonazole levels over time for Dose 1 and Dose 2. The x-axis represents Time (h) from 0 to 20, and the y-axis represents Vorticonazole levels (mg/L) from 0 to 6. The blue line represents Dose 1, and the red line represents Dose 2.](image-url)
A real patient

- 7 y/o who had a cerebellar brain tumor resected
- 25 kg, BMI 18.3 (92%), z-score 1.38 → overweight/borderline obese
- Developed an infection of the cavity with MRSA (vancomycin MIC 0.5 mg/L)
- Repeatedly culture positive and continually febrile for a week
- Primary team dosing vancomycin up to 80 mg/kg/day divided every 6 hours (500 mg/dose)
- Typical doses are 40-60 mg/kg/day
- Highest trough was 7.7 mg/L. Target was 15-20 mg/L
Fit and plan

2 gm/day, 17.8 mg/L
Results

2 gm/day, 19 mg/L
8% error
Summary

• Lipophilicity is not predictive of needed dosing modifications
• PBPK for drug development and general dosing guidance
  • More work needed on physiologic changes associated with obesity
• Pop PK with individual Bayesian control for patient care
Citations


Citations


Citations


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*Current