Pediatrics PRN Focus Session—Best Practices for Pharmacokinetics and Pediatric Dosing Strategies
Activity Number: 0217-0000-16-140-L01-P, 1.50 hours of CPE credit; Activity Type: A Knowledge-Based Activity

Tuesday, October 25, 2016
1:30 p.m. to 3:00 p.m.
Great Hall 6

Moderator: Christina Cox, Pharm. D., BCPS, BCPPS
Assistant Professor-Pediatrics, South Carolina College of Pharmacy, Columbia, South Carolina

Agenda

1:30 p.m. Ahead of the Curve! Optimizing Vancomycin Dosing with Pharmacokinetic Modeling
Jennifer Le, Pharm. D., MAS, BCPS-ID
Professor of Clinical Pharmacy, University of California San Diego, Skaggs School of Pharmacy and Pharmaceutical Sciences, La Jolla, California

2:15 p.m. Tipping the Scales: Pediatric Obesity and Is Implications for Drug Dosing
Roxane Carr, Pharm. D., BCPS
Clinical Leader, Children's & Women's Health Centre of British Columbia, Vancouver, British Columbia, Canada

Conflict of Interest Disclosures
Roxane Carr: no conflicts to disclose
Christina Cox: no conflicts to disclose
Jennifer Le: Consultancies: (Cempra), Grants: (National Institutes of Health, Memorial Medical Foundation)

Learning Objectives

1. Apply pharmacokinetic modeling to estimate area-under-curve (AUC) through the Bayesian dosing approach for vancomycin use in children.
2. Demonstrate AUC calculation to allow for use of AUC/minimum inhibitory concentration (MIC) as a primary measure of pediatric vancomycin efficacy and predictor of nephrotoxicity.
3. Evaluate optimal pharmacokinetic practice strategies and application of data to direct appropriate dosing and monitoring recommendations of vancomycin use in children through utilization of patient care scenarios.
4. Evaluate methods for dosing medications, including body surface area, total body weight, actual body weight and other correction factors.
5. Describe pharmacokinetic and pharmacodynamics differences in overweight and obese children.
6. Compare and contrast strategies to formulate appropriate dosing recommendations for overweight and obese children through application of patient scenarios.
Self-Assessment Questions

Self-assessment questions are available online at www.accp.com/am
Pediatric PRN Focus Session: Best Practices for Pharmacokinetics and Pediatric Dosing Strategies

Ahead of the curve! Optimizing Vancomycin Dosing with Pharmacokinetic Modeling

Jennifer Le, Pharm.D., MAS, BCPS-AQ ID, FCCP, FCSHP
Professor of Clinical Pharmacy
University of California San Diego, Skaggs School of Pharmacy
October 23, 2016

Conflict of Interest

• Dr. Le declares no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including employment, gifts, stock holdings, and honoraria.
• Dr. Le has previously received investigator-initiated research funding from the National Institutes of Health, Pfizer, Astellas and Cubist; served as a consultant for Pfizer and Cempra.
• Research studies presented were funded by NIH/NIAID 5K23AI089978 (Le).

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Structure

• Background
  • Population-based Pharmacokinetic Modeling
  • Bayesian Estimation
  • Monte Carlo Simulation
• Recent Literature on Vancomycin
• Clinical Practice Implications

Background

• PK differences between adults and pediatrics
• PK differences within pediatric age groups
  • Pediatrics: Birth to 18 yr
  • Preemies: < 37 weeks gestation
  • Neonates: < 1 mo
  • Infants: 1-12 mo
  • Children: 1-12 yr
  • Adolescents: 13-18 yr

Less predictable drug exposure-response relationship
Unexpected responses
Drug effects in adults may NOT be similar in children
Pediatric Clinical Studies
- Pharmacokinetic-pharmacodynamic (PK-PD) exposure targets for efficacy
  - Preclinical models
  - Limited human clinical investigations
  - Retrospective and in adults only
  - No well-designed, published studies to-date in the U.S.
    that validate PK-PD targets in actual pediatric patients
  - PK-PD targets ideally account for:
    - Physiologic development
    - Immunologic development
    - Protein binding

Pediatric Clinical Studies
- Strategies to overcome challenges
  - Opportunistic study design
    - Clinical indication
    - Samples - scavenged or coincide with routine labs
    - Sparse sampling
    - Population-based PK modeling
      - Reduce number of blood draws
      - Require large sample size
    - Dried blood spot technique
      - No centrifugation or freezing of samples
      - 15-30 μL of whole blood (20 times lower)
      - Concentration 15% lower than plasma
    - Limited number of studies (metronidazole in infants)

Opportunistic Study Design
- Provides valuable data by capitalizing on standard-of-care procedures (sample collection)
  - Low risk to participants
  - High enrollment rates
  - Useful where legislation mandates studies
  - Allows developmental PK across a wide age spectrum to compare the pharmacodynamics of various dosing strategies

Systematic Clinical Pharmacology
- Optimize dose
- Minimize sample size
  - Adult population PK data: Phase 1 or 2 studies with healthy volunteers and intense sampling (WinNonLin or NONMEM)
  - Identify PK-PD surrogate therapeutic target (e.g., T>MIC)
  - Plasma, bronchial fluid, murine model of efficacy
  - Extract data from investigator’s brochure or current literature
  - Scale models to children: size + maturation (and others as applicable)
  - Optimize pediatric dosing to maximize PK-PD target for efficacy
  - Conduct PK trials to confirm predictions

Population-Based PK (PopPK) Modeling
- FDA defines as “study of the sources and correlates of variability in drug concentrations among individuals who are the target patient population receiving clinically relevant doses of a drug of interest.”
- Supported by FDA 1999 and EMEA 2006
- Understand the factors leading to variability in PK-PD response for appropriate drug use & trial design
- Provides a quantitative estimation of drug volume of distribution, clearance, inter- & intra-subject variabilities
- Allows unbalanced study designs
- Applied in opportunistic designs to capitalize on sparse data (or a combination of sparse and intensive), which is encountered in clinical practice

PopPK vs Traditional Approaches
- Population PK-PD
  - Sparse sampling
  - Pooled data
  - Diverse population
  - Relevant results
  - Complex data analysis
  - Exploratory
- Traditional PK-PD
  - Extensive sampling
  - Single small study
  - Homogenous population
  - Extrapolate results
  - NCA
  - Confirmatory
PopPK Modeling: Pediatric Size

- Pediatric drug dosing by:
  - Age: physiologic maturation & organ function
  - Body size: weight-adjusted (mg/kg or mcg/kg)
  - Body Size — Using Adult Data for Pediatric Studies
    - Drug distribution by total body weight

\[ V_{\text{Child}} = V_{\text{Adult}} \times \left( \frac{WT}{70kg} \right)^1 \]

Abbreviations: \( V \) = Volume, \( WT \) = Weight

Bayesian Estimation

- A Priori Data
  - Population PK model
  - Inter- and intra-subject variability

- Bayesian Analyses
  - Individual PK estimates
  - Dosing

- A Posteriori Data
  - Dosing history
  - Measured serum concentrations

- Schumacher 1984
- Spiegelhalter 2000

PopPK with Bayesian Estimation

- Conducted in pediatrics for drug efficacy and safety
- Compared with standard statistical analysis of PK data, Bayesian estimation allows for more accurate quantification of parameters of interest
  - \( V_d \) and \( CL \) that can then be used to estimate \( AUC_{24} \) and trough concentrations
  - Predictive statements can be more easily derived

Monte Carlo Simulation (MCS)

- Powerful pharmacological tool used to associate drug exposure to an outcome (i.e., efficacy or adverse event)
- Provides convincing objective evidence of the merits of a proposed study design and analysis
- Integrates existing knowledge
- Uses virtual subjects
- Predicts best drug dose for PK study
- Selects the study design that will best meet the study objectives

Probability of Target Attainment (PTA)

Recent Literature on Vancomycin
Vancomycin Efficacy

- Vancomycin is the primary treatment for serious infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) in hospitalized adults and children
- Studies in adults support use of vancomycin at
  - $\text{AUC}_{24} \cdot \text{MIC} (\text{or} \ \text{AUC:MIC}) \geq 400 \ \text{mg-hr/L}$, albeit recent studies suggest lower exposure target
  - Trough concentration (or Cmin) $\sim 15 - 20 \ \text{mcg/mL}$
- Recent studies in children
  - $\text{AUC}_{24} \cdot \text{MIC} \geq 400$ is more achievable in children
  - Trough concentration (or Cmin) $\sim 9 - 10 \ \text{mcg/mL}$

Monte Carlo Simulation (MCS) with Bayesian Estimation: Correlation $\text{AUC}_{24}$ and Trough at 60 mg/kg/day, $N = 11,000$

Monte Carlo Simulation (MCS) with Bayesian Estimation: $\text{AUC}_{24}$ vs Trough Concentration

PopPK Modeling: Covariate Search

<table>
<thead>
<tr>
<th>Covariates for Vancomycin Clearance (L/hr)</th>
<th>Change in Minimum Objective Function (MOF) from Base Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (base model)</td>
<td>--</td>
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<tr>
<td>Weight and Scr assay</td>
<td>200</td>
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<tr>
<td>Weight and concurrent use of nephrotoxic agents</td>
<td>-85</td>
</tr>
<tr>
<td>Weight and stay in intensive care unit</td>
<td>-96</td>
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<tr>
<td>Weight and use of chemotherapeutic agents</td>
<td>-90</td>
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<tr>
<td>Weight and age groups*</td>
<td>-123</td>
</tr>
<tr>
<td>Weight and Scr</td>
<td>-177</td>
</tr>
<tr>
<td>Weight, Scr and age groups</td>
<td>-188</td>
</tr>
<tr>
<td>Weight, Scr and Log(Age) (final model)</td>
<td>-284</td>
</tr>
</tbody>
</table>

PopPK Modeling: Final Model and External Validation

Parameter Estimates for Vancomycin Clearance

- $\text{CL} (L/hr) = 0.228 \times \text{Wt}^{0.75} \times (0.48/\text{Scr})^{0.361}$

- $\text{Vd} (L) = 0.43 \times \text{Wt}$

- $\text{CL} = 10 - 25 \ \text{mg/kg/day}$

- $\text{Vd} = 11,000 \ \text{mg/kg}$

- *Internal Validation:* Uncertainty was evaluated using a bootstrap analysis ($N=1000$) to estimate the posthoc Bayesian Vd and CL, which were within the 95% confidence intervals

- *External Validation:* Vd and CL formulas were validated by different investigator (Ploessle et al)
Vancomycin Empiric Dose

- Early studies suggest 60 mg/kg/day (Bayesian, old serum creatinine assay) to 70 mg/kg/day (non-Bayesian).
- PopPK with Bayesian estimates & Monte Carlo simulations
  - Incorporated new serum creatinine assays and E-test
  - Depending on age (3mo – 21yo), serum creatinine, and MIC distribution:
    - 60 to 70 mg/kg/day every 6 hr
    - Dosing is warranted if:
      - 3 months to < 2 years old
      - Serum creatinine < 0.45 mg/dL (for 2 to 12 years old)
      - 30% MRSA isolates have MIC ≥ 1.5 mcg/mL.
- Less frequent dosing at 15 mg/kg every 8 hr (45 mg/kg/day) for children with renal impairment.

Vancomycin Empiric Dose

- Children without (control) and with renal impairment (case)
- Remember to monitor SCr as may need to readjust dose.

Vancomycin Empiric Dose: Calculation

**AUC Approach**

- Dose_{24h} = AUC_{24h}/MIC * CLVanco
  - Estimate CLVanco using published popPK estimate
  - If total daily dose remains the same, smaller doses with shorter intervals does not alter AUC_{24h}/MIC but does increase trough concentration

**Peak-Trough Approach**

- Nomogram
  - Predefined dose in mg/kg
  - Determine dosing interval by k_{el}
  - Intermittent PK Models
    - Short infusion model
    - Bolus model
    - Calculate patient dose based on target peak/trough concentrations
  - Estimate V_{d} and CLVanco using published popPK estimates

Regardless of targeted AUC_{24h} or trough concentration, consider alternative therapy for invasive infections caused by MRSA with MIC ≥ 2 mcg/mL to prevent treatment failure.

Vancomycin Loading Dose

- Improved treatment success when first trough is within therapeutic range
- Fewer patients achieved target first trough when loading dose is not used
- Load using 20 mg/kg by total (actual) body weight in non-obese (control) and obese (case) children improved PTA within first 12 hr.

Vancomycin Nephrotoxicity: Multivariate Analysis

- PopPK model with Bayesian estimations
- Vancomycin serum troughs ≥ 15 mcg/mL in children is associated with a 3-fold (28% vs 7%) increase by multivariable regression
- Analysis of 680 subjects with 1,576 vancomycin concentrations

- Risk of nephrotoxicity
  - C_{min} ≥ 15 mcg/mL
  - aOR 2.5 (1.1–5.8; P = .028)
  - AUC ≥ 800 mg-h/L
  - aOR 3.7 (1.2–11.0; P = .018)
  - Adjusted for ICU and nephrototoxic drugs
Therapeutic Vancomycin Monitoring Current Practice

- 2009 ASHP/IDSA/SIDP Consensus Recommendations for ADULTS
  - Trough 15–20 mcg/mL to predict AUC<sub>24</sub> of 400 (assuming MIC of 1)
- Pediatrics: IDSA MRSA guidelines
  - Limited data; consider trough target 15–20 mcg/mL
- Challenges in pediatrics
  - Current monitoring strategy
    - Mainly trough concentration, some use AUC<sub>24</sub>

AUC<sub>24</sub>: Trapezoidal Method

- Calculate each individual trapezoid:
  \[ \frac{C_1 - C_2}{2} \times \Delta t \]
- Sum trapezoids
- Assumes line between data points
- NOT practical method

AUC<sub>24</sub>: Equation Method

- Dose Approach (Pediatrics - Le 2014; Le 2013)
  - \[ \text{AUC}_{24} = \text{Dose}_{24} \times CL \]
  - Calculate CL using estimated peak
  - Use two post-distribution concentrations
    - \[ k_n = \ln(C/C_0) / \text{atime} \]
    - Use total daily dose

- Concentration Approach (Adults - Pai 2014)
  - Overpredict
    - \[ \left( \frac{C_{\text{max}} - C_1}{k_n} \right) + C_1 \]
    - \[ C_{\text{max}} = \text{back-extrapolate to start of infusion} \]
  - Underpredict
    - \[ \left( T_{\text{inf}} \times \left( C_{\text{max}} + C_1 / 2 \right) \right) + \left( C_{\text{max}} - C_1 / k_n \right) \]
    - \[ C_{\text{max}} = \text{back-extrapolate to end of infusion} \]
  - Multiply by interval/day = AUC<sub>24</sub>

AUC Monitoring: Bayesian Methods

- Computerized (software) application of Bayes theorem
- Software with Bayesian analysis
  - BestDose, MwPharm, T.D.M.S. 2000
- Trough (1) versus Peak-Trough (2) Sampling
  - 97% accuracy using trough only in adults with 60% achieving AUC ≥ 400 have trough < 15 mcg/mL
- Peak-Trough sampling improved accuracy & precision of AUC<sub>24</sub> and CL in pediatrics
- Bayesian is superior to non-Bayesian Estimation (which may under-predict AUC)

Accuracy AUC Monitoring: Bayesian Methods

- PopPK model with Bayesian estimations
- Analysis of 138 subjects with 712 vancomycin concentrations
- Compared with 15, the 25 sampling for vancomycin improved accuracy and precision in estimating and predicting future AUC<sub>24</sub>
- Evaluate two drug concentrations to ensure adequate drug exposure

Clinical Practice Implications
**Patient Case**

- 6.3-year-old boy (weight 16 kg, height 106 cm, BSA 0.686 m²) previously healthy
- Admitted to ICU for right upper lobe pneumonia (confirmed by CxR) requiring mechanical ventilation
- Laboratory values:
  - WBC: 22.2 x 10⁹ cells/mm³, 80% neutrophils; 11% bands
  - SCR: 0.40 mg/dL
- Empiric therapy:
  - Ceftriaxone 800 mg (~50 mg/kg) intravenously every 24 hours
  - Vancomycin 210 mg (~13 mg/kg) intravenously every 6 hours

**Patient Case: Empiric Dose AUC₂⁴**

- Empiric Dosing Regimen: Population-based PK
  - Vd (L) = 0.636 * Wt = 10.18 L
  - CL (L/hr) = 0.248 * Wt⁰.⁷⁹*(0.48/Scr)⁰.³⁰⁶*ln(Age)/7.8⁰.⁹⁹⁵
    = 2.10 L/hr = 0.13 L/hr/kg
  - AUC₂⁴ = Dose₂⁴ / CL
    \( k_e = 0.206 \text{ hr}^{-1} \); \( t_{1/2} = 3.4 \text{ hr} \)
  - AUC₂⁴ = 840 mg * 2.10 L/hr = 140 mg/hr/L

**Patient Case: Revised Dose AUC₂⁴**

- Revised Dosing Regimen: Patient-specific PK
  - AUC₂⁴ = Dose₂⁴ / CL

**Antimicrobial Stewardship Program**

Vancomycin prescription data were collected from 2008 Quarter 1 through 2013 Quarter 3, and the Vancomycin ASP intervention was initiated in 2009 Quarter 2 (red dashed line).

**Conclusions**

- PopPK with Bayesian estimation and Monte Carlo simulations are supported by the FDA and EMEA for drug evaluations in pediatrics.
- Monitoring AUC₂⁴, particularly via Bayesian methods, may be better than troughs to improve clinical response and minimize risks in pediatrics.
- Assess both AUC and trough concentrations, using the minimum effective dose to optimize efficacy and minimize nephrotoxicity.
- For MRSA with MIC ≥ 2 mg/L, an alternative antibiotic should be considered.
Future Direction

• PK/PD-guided studies to evaluate clinical and bacteriological outcomes
• Optimal PD exposure targets (e.g., AUC24/MIC ratios or trough concentrations) to reliably predict the clinical response
• Neonates vs children vs adolescents
• MRSA and coagulase-negative Staphylococci
• Bacteremia, pneumonia, endocarditis, osteoarticular infections
• Integration of antimicrobial stewardship program to decrease vancomycin use, especially in patients with negative cultures on vancomycin beyond 48–72 hr

Acknowledgement

Research Funding
Active: JMI Laboratories (Le)
NIH/NICHD U54-HD071600 (Nizet/Capparelli)
Previous: NIH/NIAID 5K23AI089978 (Le); NIH/NICHD 2011-POP01 (Benjamin); Cubist, Pfizer and Astellas

Contact Information
Jennifer Le, PharmD, MAS, BCPS-ID, FCSHP, FCCP
Professor of Clinical Pharmacy
University of California, San Diego
Skaggs School of Pharmacy and Pharmaceutical Sciences
Email: jenle@ucsd.edu or leoffice@ucsd.edu
LinkedIn, Research Gate, Twitter @idpedle, E-Scholarship
Website: http://pharmacy.ucsd.edu/faculty/le.shtml

Thank You!
Tipping the Scales: Pediatric Obesity and Its Implications for Drug Dosing

Roxane Carr, BSc(Pharm), PharmD, ACPR, BCPS, FCSHP
Children’s & Women’s Health Centre of BC
University of British Columbia
Vancouver, BC, Canada
October 25, 2016

Learning Objectives

• Evaluate methods for dosing medications, including body surface area, total body weight, ideal body weight and other correction factors.
• Describe pharmacokinetic and pharmacodynamic differences in overweight and obese children.
• Compare and contrast strategies to formulate appropriate dosing recommendations for overweight and obese children through application of patient scenarios.

Introduction

• 2012 US children:
  • 6-11 years old: 18% obese
  • 12-19 years old: 21% obese
  • > 1/3 of all children and adolescents were overweight or obese
• 2013 WHO estimated that worldwide:
  • 42 million children aged < 5 years were overweight
  • 75% of those lived in developing countries

Definitions

<table>
<thead>
<tr>
<th></th>
<th>Overweight</th>
<th>Obese</th>
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</thead>
<tbody>
<tr>
<td>WHO</td>
<td>BMI for age &amp; sex Z score ≥ 1 SD (85th percentile)</td>
<td>BMI for age &amp; sex Z score ≥ 2 SD (97th percentile)</td>
</tr>
<tr>
<td>American Academy of Pediatrics</td>
<td>BMI for age &amp; sex &gt; 85th percentile</td>
<td>BMI for age &amp; sex &gt; 95th percentile</td>
</tr>
<tr>
<td>Others</td>
<td>BMI for Age &gt; 95th percentile</td>
<td></td>
</tr>
</tbody>
</table>

Age range

- 5-19 years
- > 2 years

Conflict of Interest

• No conflict of interest to declare.

Introduction

• 5 year old boy admitted Friday evening
• Fell in to septic tank, unknown period of time down before found (max 40 min)
• At scene: GCS 6 and had seizure, multiple fractures
• Intubated & ventilated
• Mediations:
  • Morphine 20 mcg/kg/hour IV
  • Midazolam 360 mcg/kg/hour IV
• Concerns re: hypoxic injury and severe brain damage/possible brain death raised
Case cont...
- Looking at the child he seems “really big for his age”
- Weight: 40 kg (88 pounds)
- Height: 115 cm (3 ft 9in)

BMI: Body Mass Index
- BMI = \( \frac{\text{weight (kg)}}{\text{height (cm)}^2} \)
- Calculation same for adults & children
- Interpretation differs:
  - As child grows, amount of body fat changes with age
  - Need to interpret child BMI in relation to age

Case cont...
- Confirm his age is correct
- Check Growth Chart:
  - Weight: 40 kg (88 pounds) (> 97th percentile)
  - Height: 115 cm (3 ft 9in) (90th percentile)

BMI Calculation
- BMI Calculator for Child and Teen

Case cont...
- 5 year old boy admitted 2 & 1/2 days ago
- Medications:
  - Morphine 20 mcg/kg/hour IV
  - Midazolam 360 mcg/kg/hour IV
- Concerns re: hypoxic injury and severe brain damage/possible brain death raised
- Any drug related problems?
**Body Composition**

- Obese children have ↑:
  - Height (3.9 cm = 1.5 inches)
  - TBW
  - Body volume
  - Lean Mass & more hydrated (↑ ECF)
  - Fat mass: 30-50% of total weight and 73% excess weight
  - Bone mineral content

*Int J Obes 2006; J Appl Physiol 1995*

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**Absorption**

- Obese Adults: Not shown to be modified
- Obese children: No information comparing absorption in obese versus non-obese children

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**Distribution**

**Obese adults:**
- Variable, drug-dependent
- Lipophilic drugs:
  - ↑ Vd
- Hydrophilic drugs:
  - ↓ Vd/TBW

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**Obese children:**
- No information re: changes in regional blood flow
- ↑ absolute lean body mass and fat mass
- ↓ % lean tissue per kg/TBW
- ↑ % fat tissue
- Protein binding: very limited information

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**General Pharmacokinetic Differences in Obese Children**

- Lipophilic drugs:
  - ↑ Vd/TBW
- Hydrophilic drugs:
  - ↓ Vd/TBW

*But... relationship between Vd & ↑ hydration of lean mass in obese children unknown*
Metabolism
• Difficult to assess!!

Obese adults:
• ↑ Oxidation
• ↑ Conjugation of lorazepam & oxazepam

Metabolism
Obese children
• Influence of obesity on major phase 1 & phase 2 metabolic pathways in children unknown

Excretion
• Tubular secretion:
  • No information in adults or children

• Tubular reabsorption:
  • No information in adults or children

Excretion
GFR:
• Adults:
  • Higher GFR in obese adults than non-obese adults
  • Salazar-Corcoran equation – validated to estimate GFR in obese adults

Excretion
Salazar-Corcoran equation
Males: \( \text{CrCl}_{\text{est}} = (137 - \text{age}) \times [(0.285 \times \text{Wt}) + (12.1 \times \text{Ht}^2)] \)
51 \times \text{SCR}

Females: \( \text{CrCl}_{\text{est}} = (146 - \text{age}) \times [(0.287 \times \text{Wt}) + (9.74 \times \text{Ht}^2)] \)
60 \times \text{SCR}

Wt = weight (kg)
Ht = height (m)
SCR = serum creatinine (mg/dL)

Orthopedics 2006

Excretion
GFR:
• Children:
  • SCR may be higher or no different in obese vs non-obese children
  • No validated equations to estimate GFR in obese children

J Pediatr Pharmacol Ther 2010
Methods for Dosing Medications in Children
- Age based
- Allometric scaling
- Body surface area (BSA) based
  - Mosteller BSA = \(\frac{\text{height (cm)} \times \text{weight (kg)}}{3600}\)
- Weight based

Methods for Dosing Medications in Overweight & Obese Children

Weight & Size Descriptors
- Total body weight (TBW)
- Lean body weight (LBW)
- Ideal body weight (IBW)
- Adjusted body weight (ABW)/Dosing body weight

Total Body Weight
- Best size descriptor for Vd in PK studies
- Impacts loading doses
- Appropriate dosing weight for:
  - Antineoplastic agents
  - Cefazolin
  - Antibiotics where TDM can be done:
    - Vancomycin
    - Aminoglycosides
  - Anticoagulants where coagulation parameters can be monitored:
    - Heparin
    - Enoxaparin
    - warfarin

Lean Body Weight (LBW)
- LBW = TBW – [fractional fat mass X TBW]
- Often used interchangeably with IBW
- Calculation of fractional fat mass
- Best size descriptor for clearance (CL) in PK studies

Ideal Body Weight
- Plays a role in weight loss targets
- Can be used as surrogate for LBW
- May be useful for dosing highly lipophilic drugs and continuous infusions
**Estimation of IBW in Children**

- McLaren Method: 50th percentile of weight for height
- Moore Method: Corresponding weight percentile for height
- BMI Method: BMI 50th percentile for age [height (cm)]

**IBW Estimation: McLaren Method**

- 50th percentile of weight for height
- Assumes weight to height ratio is a constant at a given age
- Works well for children at 50th percentile for height
- Does not account for age
- “Too tall” children: height is > 50th percentile for any age (> 163 cm girls and 177 cm boys)

**IBW Estimation: Moore Method**

- Corresponding weight percentile for height
- Calculate IBW at same SD as the child’s height for age
- Challenging to approximate if:
  - Height falls between percentiles
  - Height > 97th percentile or < 3rd percentile
IBW Estimation: BMI Method

- BMI 50th percentile for age X [height (m)]²
- Age specific
- Accounts for:
  - Adiposity rebound
  - Developmental changes in body composition during puberty and adolescence
- Compares well with weight for height and measures of body fat
- Carries into adulthood
- Needs a calculator!
- Conversion of units (pounds to kg, inches to meters)

Adjusted Body Weight (ABW)

- Dosing body weight (DBW)
- Drug specific
- Commonly used to dose aminoglycosides in adults
- Not tested in children

Approach

- Consider what is known:
  - Studies published
  - Lipophilic vs hydrophilic
  - Pharmacokinetics
  - Therapeutic index
  - Dose-related adverse effect
  - Dosing in obese adults
  - Recommended adult maximum doses
- Ability to monitor: serum/plasma concentrations, clinical outcomes

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Case
• 5 year old boy admitted Friday evening
• Fell in to septic tank, unknown period of time down before found (max 40 min)
• At scene: GCS 6 and had seizure, multiple fractures
• Intubated & ventilated
• Medications:
  • Morphine 20 mcg/kg/hour IV
  • Midazolam 360 mcg/kg/hour IV
• Concerns re: hypoxic injury and severe brain damage/possible brain death raised

Case:
• BB a 5 year old male
• TBW 40 kg
• Height 115 cm
• BMI 30.2 kg/m²
• IBW: 20 - 23 kg
• Morphine 20 mcg/kg/hour IV
• Midazolam 360 mcg/kg/hour IV
• Unresponsive

Case: Morphine
• Lipophilic
• Vd 4.7 L/kg
• Therapeutic index: narrowish
• Dose related ADRs: Yes but patient intubated and ventilated
• Adult information: limited
• Recommended adult maximum dose: none
• Monitoring: clinical yes

Which weight to use?

Case:
• Morphine

Recommendation: Shut off for neuro assessment

Restart consider IBW “equivalent” e.g., if IBW 20 kg patient receiving 40 mcg/kg/hour IV morphine – high dose!

Case: Vancomycin Dosing
Vancomycin:
• Hydro & lipophilic: distributes into TBW & tissues
• PK:
  • Vd 0.57 L/kg range 0.26-1.05 L/kg
  • Renal elimination
• Therapeutic index: narrowish
• Dosing in obese adults: TBW
• Ability to monitor: serum concentration(s)
**Case: Vancomycin Dosing**

- Vancomycin – which weight to use?
- TBW
- Interval based on renal function
- Therapeutic drug monitoring

(Clin Pediatr 2011; Am J Health Syst Pharm 2011; Pharmacotherapy 2013)

**Case: Meropenem Dosing**

Meropenem:
- Hydro & lipophilic: distributes into TBW & tissues
- PK:
  - Vd 0.3-0.4 L/kg
  - Renal elimination (70%)
  - Metabolized in plasma (20%)
- Therapeutic index: wide
- Dose related ADRs: seizures
- Dosing in obese adults: Vd & CL similar; no need to adjust dose for body weight (500mg – 2g IV q8h)
- Ability to monitor: not easily

**Case: Meropenem Dosing**

Meropenem: TBW vs IBW?

**TBW: 40 kg**
- Standard dosing (60 mg/kg/day) = 800 mg IV q8h
- Meningitic dosing (120 mg/kg/day) = 1600 mg IV q8h

**IBW: 20 kg**
- Standard dosing = 400 mg IV q8h
- Meningitic dosing = 800 mg IV q8h

**Summary**

- Volume of distribution most impacted by obesity
- Total body weight best descriptor for loading doses
- Lean body weight best descriptor for clearance
- Several methods for calculating IBW
- Have an approach as data limited!!