Ontogeny of Renal Function:
Application in Population-Based Modeling for Drug Development

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Disclosure Statement

• I have no financial relationships to disclose relating to this presentation

• The views expressed in this talk represent my opinions and do not necessarily represent the views of FDA
Outline

• Renal Maturation Models
  – Overview
  – Evaluation with drug PK data
  – Challenges and opportunities

• Bedside Renal Function Equations
  – Overview
  – Evaluation with drug PK data
  – Challenges and opportunities

*Focus: Newborns and infants / Application in drug development*
Renal Function and Glomerular Filtration Rate

- Normal Level of GFR Varies by Age

<table>
<thead>
<tr>
<th>Normal GFR in Children and Adolescents</th>
<th>Mean GFR ± SD (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Sex)</td>
<td></td>
</tr>
<tr>
<td>1 wk (males and females)</td>
<td>41 ± 15</td>
</tr>
<tr>
<td>2-8 wk (males and females)</td>
<td>66 ± 25</td>
</tr>
<tr>
<td>&gt;8 wk (males and females)</td>
<td>86 ± 22</td>
</tr>
<tr>
<td>2-12 y (males and females)</td>
<td>130 ± 27</td>
</tr>
<tr>
<td>13-21 y (males)</td>
<td>140 ± 30</td>
</tr>
<tr>
<td>13-21 y (females)</td>
<td>126 ± 22</td>
</tr>
</tbody>
</table>

NKF-K/DOQI Classification of the Stages of CKD

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR (mL/min/1.73 m²)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt;90</td>
<td>Kidney damage with normal or increased GFR</td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
<td>Kidney damage with mild reduction of GFR</td>
</tr>
<tr>
<td>3</td>
<td>30-59</td>
<td>Moderate reduction of GFR</td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>Severe reduction of GFR</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15 (or dialysis)</td>
<td>Kidney failure</td>
</tr>
</tbody>
</table>

Current Population PK Modeling Approach

- A review based on 61 articles reporting PopPK models from 13 renally eliminated drugs
- Intention: to separate the effects of body size, age and kidney function on drug clearance

*Key physiological components*

\[ CL = CL_{\text{standard}} \times F_{\text{size}} \times F_{\text{maturation}} \times F_{\text{kidney}} \]

*Note:* \( F_{\text{kidney}} \) accounts for deviation from normal kidney function, e.g., due to inflammatory disease or drug-related nephrotoxicity.

*Wilbaux et al, J Clin Pharm 2016, 56(8) 909–935*
Key physiological components

Body size
WT

Ante-natal development
GA

Post-natal maturation
PNA

Kidney function
SCr

\[ CL = CL_{standard} \times F_{size} \times F_{maturation} \times F_{kidney} \]

\[ F_{size} = \left( \frac{WT}{WT_{std}} \right)^{0.75} \]

\[ F_{maturation} = \frac{PMA_{Hill}^{TM_{50}}}{TM_{50}^{Hill} + PMA_{Hill}} \]

TM_{50} = 47.7, Hill = 3.4

\[ F_{kidney} = \left( \frac{GFR_{actual}}{GFR_{std}} \right)^{PWR} \]

\[ F_{kidney} = \left( \frac{1}{Scr_{actual}} \right)^{PWR} \]

\[ F_{kidney} = \left( \frac{Scr_{actual}}{Scr_{std}} \right)^{PWR} \]

Combined linear and power function*

\[ F_{maturation} = (1 + \theta_{GACL} \cdot GA) \cdot (1 + PNA^{PWR}) \]

Wilbaux et al, J Clin Pharm 2016, 56(8) 909–935
Human renal function maturation: a quantitative description using weight and postmenstrual age

Malin M. Rhedin · Brian J. Anderson · A. Michael Peters · Malcolm G. Coulthard · Barry Wilkins · Michael Cole · Etienne Chatelut · Anders Grubb · Gareth J. Veal · Michael J. Keir · Nick H. G. Holford

Maturation based on PMA

No efforts were made to distinguish pre-term and full-term neonates

Table 1 Summary of pooled data used in the study

<table>
<thead>
<tr>
<th>Characteristics of the study</th>
<th>Study</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method</td>
<td></td>
<td>Cr-EDTA</td>
<td>Cr-EDTA</td>
<td>Mannitol</td>
<td>Inulin</td>
<td>Inulin</td>
<td>Cr-EDTA</td>
<td>Iohexol</td>
<td>Sinistrin</td>
</tr>
<tr>
<td>Number</td>
<td></td>
<td>185</td>
<td>347</td>
<td>63</td>
<td>39</td>
<td>56</td>
<td>111</td>
<td>85</td>
<td>37</td>
</tr>
<tr>
<td>Mean PNA (range)</td>
<td></td>
<td>(0.9–14.2)</td>
<td>(0.17–31)</td>
<td>(2–days-11-years)</td>
<td>(2–63)</td>
<td>(1–80)</td>
<td>(2.4–22.8-year)</td>
<td>(0.3–17)</td>
<td>(0.5–33)</td>
</tr>
<tr>
<td>Mean weight (range)</td>
<td></td>
<td>(22.5 kg–45.4 kg)</td>
<td>(41.9 kg–120.6 kg)</td>
<td>(10.8 kg–2.4–36)</td>
<td>(1.6 kg–0.68–3.71)</td>
<td>(1.5 kg–0.64–4.65)</td>
<td>(44.6 kg–9.6–89)</td>
<td>(40.1 kg–5.4–98.5)</td>
<td>(1.1 kg–0.62–1.9)</td>
</tr>
<tr>
<td>Mean GFR (range)</td>
<td></td>
<td>(107 ml/min–25 ml/min)</td>
<td>(131 ml/min–25 ml/min)</td>
<td>(122 ml/min–50 ml/min)</td>
<td>(29 ml/min–60 ml/min)</td>
<td>(25 ml/min–108 ml/min)</td>
<td>(108 ml/min–120 ml/min)</td>
<td>(120 ml/min–23 ml/min)</td>
<td></td>
</tr>
<tr>
<td>Sex reported</td>
<td></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>More than one observation/ subject</td>
<td></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
<td>No diagnoses available</td>
<td>Oncology</td>
<td>Normal, well children</td>
<td>Premature</td>
<td>Premature</td>
<td>Nephrology</td>
<td>No known renal disease</td>
<td>Premature</td>
</tr>
</tbody>
</table>

GFR Glomerular filtration rate; PMA postmenstrual age; PNA postnatal age
# Collected PK Data from Renally Eliminated Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total Clearance (L/h)</th>
<th>Renal Clearance (L/h)</th>
<th>% Renal Clearance</th>
<th>Contribution of Non-renal Elimination Pathways</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>6.0 ± 0.5</td>
<td>5.0 ± 0.9</td>
<td>94%</td>
<td>&lt;5% metabolism</td>
</tr>
<tr>
<td>Gadobutrol</td>
<td>6.2</td>
<td>6.2</td>
<td>&gt;99%</td>
<td>No metabolism</td>
</tr>
<tr>
<td>Gadoterate</td>
<td>7.1</td>
<td>7.1</td>
<td>&gt;99%</td>
<td>No metabolism</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>5.9 ± 1.5</td>
<td>5.3 ± 2.0</td>
<td>&gt;90%</td>
<td>~ 10% metabolism</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>16.9 ± 3.3</td>
<td>10.4 ± 3.7</td>
<td>61%</td>
<td>10% Biliary elimination; Likely secretion</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>6.0 ± 1.8</td>
<td>4.6 ± 1.5</td>
<td>~77%</td>
<td>No data</td>
</tr>
<tr>
<td>Meropenem</td>
<td>14.6 ± 8.3</td>
<td>10.4 ± 6.4</td>
<td>71%</td>
<td>Likely secretion; ~30% metabolism</td>
</tr>
<tr>
<td>Netilmicin</td>
<td>5.5 ± 0.8</td>
<td>4.0 ± 0.6</td>
<td>72%</td>
<td>No data</td>
</tr>
</tbody>
</table>

*Wang et al., Clin Pharmacol Ther. 2018*
### Distribution of Newborns and Infants in Age Categories

<table>
<thead>
<tr>
<th>Drugs (n)</th>
<th>≥ 42 weeks PMA (n)</th>
<th>37 to &lt;42 weeks PMA (n)</th>
<th>&lt;37 weeks PMA (n)</th>
<th>PNA (Days)</th>
<th>GA (Weeks)</th>
<th>PMA (Weeks)</th>
<th>Body Weight (kg)</th>
<th>SCR (mg/dL)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin (108)</td>
<td>22</td>
<td>11</td>
<td>75</td>
<td>10 (3-625)</td>
<td>29 (23-41)</td>
<td>31 (25-127)</td>
<td>1.29 (0.45-11.28)</td>
<td>0.38 (0.2-0.96)</td>
</tr>
<tr>
<td>Gadobutrol (43)</td>
<td>39</td>
<td>4</td>
<td>0</td>
<td>212 (6-696)</td>
<td>40 (40-40)</td>
<td>70 (41-139)</td>
<td>7.2 (2.80-14.20)</td>
<td>0.27 (0.1-0.66)</td>
</tr>
<tr>
<td>Gadoterate (45)</td>
<td>41</td>
<td>4</td>
<td>0</td>
<td>266 (4-721)</td>
<td>40 (40-40)</td>
<td>78 (39-143)</td>
<td>8.00 (3.00-15.00)</td>
<td>0.24 (0.14-0.42)</td>
</tr>
<tr>
<td>Vancomycin (92)</td>
<td>22</td>
<td>31</td>
<td>39</td>
<td>13 (2-367)</td>
<td>36 (24-41)</td>
<td>39 (25-89)</td>
<td>2.61 (0.53-8.26)</td>
<td>0.5 (0.18-1.67)</td>
</tr>
<tr>
<td>Ampicillin (73)</td>
<td>5</td>
<td>31</td>
<td>37</td>
<td>2 (0-24)</td>
<td>36 (24-41)</td>
<td>37 (25-43)</td>
<td>2.47 (0.50-4.19)</td>
<td>0.6 (0.2-2.5)</td>
</tr>
<tr>
<td>Gentamicin (143)</td>
<td>46</td>
<td>48</td>
<td>49</td>
<td>1 (0-711)</td>
<td>37 (23-43)</td>
<td>38 (23-135)</td>
<td>3.12 (0.40-12.00)</td>
<td>0.6 (0.18-5.5)</td>
</tr>
<tr>
<td>Meropenem (200)</td>
<td>13</td>
<td>31</td>
<td>156</td>
<td>21 (1-92)</td>
<td>28 (23-40)</td>
<td>32 (24-51)</td>
<td>1.54 (0.39-6.50)</td>
<td>0.5 (0.1-1.9)</td>
</tr>
<tr>
<td>Netilmicin (83)</td>
<td>1</td>
<td>3</td>
<td>79</td>
<td>10 (2-121)</td>
<td>27 (23-41)</td>
<td>29 (24-43)</td>
<td>1.00 (0.47-3.00)</td>
<td>0.77 (0.27-1.67)</td>
</tr>
<tr>
<td>All drugs (787)</td>
<td>189</td>
<td>163</td>
<td>435</td>
<td>13 (0-721)</td>
<td>33 (23-43)</td>
<td>35 (23-143)</td>
<td>2.16 (0.39-15.00)</td>
<td>0.5 (0.1-5.5)</td>
</tr>
</tbody>
</table>

*Wang el al., Clin Pharmacol Ther. 2018*
Predictive Performance for Drug Clearance Using PMA based Model (1)

Wang et al., Clin Pharmacol Ther. 2018
Predictive Performance for Drug Clearance Using PMA based Model (2)
Renal Maturation Model in Drug Development

• Case Example:
  – Gadobenate dimeglumine; gadolinium-based contrast agent with ~95% renal elimination
  – PK simulations based on the PMA-based maturation model were used to inform the dose selection in infants

**Pediatric:** A population pharmacokinetic analysis incorporated data from 25 healthy subjects (14 males and 11 females) and 15 subjects undergoing MR imaging of the central nervous system (7 males and 8 females) between ages of 2 and 16 years. The subjects received a single intravenous dose of 0.1 mmol/kg of MultiHance. The geometric mean $C_{\text{max}}$ was 62.3 $\mu$g/mL (n=16) in children 2 to 5 years of age, and 64.2 $\mu$g/mL (n=24) in children older than 5 years. The geometric mean $AUC_{0-\infty}$ was 77.9 $\mu$g·h/mL in children 2-5 years of age (n=16) and 82.6 $\mu$g·h/mL in children older than 5 years (n=24). The geometric mean half-life was 1.2 hours in children 2 to 5 years of age and 0.93 hours in children older than 5 years. There was no significant gender-related difference in the pharmacokinetic parameters in the pediatric patients. Over 80% of the dose was recovered in urine after 24 hours. Pharmacokinetic simulations indicate similar $AUC$ and $C_{\text{max}}$ values for MultiHance in pediatric subjects less than 2 years when compared to those reported for adults; no age-based dose adjustment is necessary for this pediatric population.
Renal Maturation Model in Drug Development

• Opportunities:
  – Age based renal maturation models, in combination with body weight-based scaling, can be used in population modeling for drugs that are primarily eliminated via renal pathway to inform initial dose selection for newborns and infants in clinical trials.

• Challenges:
  – The current models do not incorporate renal ontogeny of reabsorption and secretion. Better understanding of the ontogeny of drug transporters and metabolism in kidney are needed.
  – The model does not account for renal impairment (due to kidney disease or drug-related nephrotoxicity).
Outline

• Renal Maturation Models
  – Overview of models (Filtration, Reabsorption, Secretion)
  – Evaluation with drug PK data
  – Challenges and opportunities

• Bedside Renal function Models
  – Overview
  – Evaluation with drug PK data
  – Challenges and opportunities
Estimation of GFR

- Traditionally used methods
  - Inulin
  - PAH (para-aminohippurate)
  - DTPA (diethylenetriamine penta-acetic acid)
- Methodology can be based on urinary accumulation or plasma disappearance
- Newer substances that have been studied in children
  - Iothalamate—non-radioactive, actively secreted by renal proximal tubule
  - Iohexol—non-radioactive, less allergenic potential
The Case for Creatinine

• Metabolic product of muscle
• Generally produced at a constant rate by the body
• Freely filtered
• Not metabolized
• BUT, is secreted by the proximal tubule
• Attractive as an estimate of GFR because injection is not necessary and steady state plasma creatinine can be used without need for collection of urine

Lynne Yao, FDA presentation, 2016
Limitations of Creatinine

• Serum creatinine affected by
  – Muscle mass
  – Muscle breakdown
  – Maternal transfer
  – Tubular secretion
  – Diet
  – Disease (e.g. neuromuscular disease, anorexia nervosa)

• These factors produce variability in specific situations, especially in preterm and newborn infants
Serum-Creatinine (SCR)-based equations for Estimation of GFR

- **Schwartz (Original)**
  - $\text{eGFR (mL/min/1.73m}^2) = k \times \text{HT (cm)}/\text{SCR (mg/dL)}$ ($k=0.33$ for LBW<1yr, 0.45 for Term <1 yr, 0.55 for >= 1 yr female, 0.70 for >= 1 yr male)
  - $k$ values from FDA Guidance: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products, 2014

- **Modified Schwartz (Bedside Schwartz)**
  - $\text{eGFR (mL/min/1.73m}^2) = k \times \text{HT (cm)}/\text{SCR (mg/dL)}$ ($k=0.413$)

- **Counahan-Barratt**
  - $\text{eGFR (mL/min/1.73m}^2) = k \times \text{HT (cm)}/\text{SCR (mg/dL)}$ ($k=0.43$)

- **Flanders Metadata**
  - $\text{eGFR (mL/min/1.73m}^2) = (0.0414 \times \log(\text{AGE}) + 0.3018) \times \text{HT}/\text{SCR}$

- **Leger**
  - $\text{eGFR (mL/min) = } (56.7 \times \text{WT} + 0.142 \times (\text{HT}^2))/(\text{SCR} \times 88.4)$

- **British Columbia Children’s Hospital**
  - $\text{eGFR (mL/min/1.73m}^2) = \exp(1.18+0.0016 \times \text{WT}+0.01 \times \text{HT}+149.5/(\text{SCR} \times 88.4)-2141/((\text{SCR} \times 88.4)^2))$

- **Lund-Malmo, applicable if SCR < 1.70 mg/dL**
  - Male: $\text{eGFR (mL/min/1.73m}^2) = \exp(4.62-0.0112 \times \text{SCR} \times 88.4-0.0124 \times \text{AGE}+0.339 \times \log(\text{AGE})$
  - Female: $\text{eGFR (mL/min/1.73m}^2) = \exp(4.62-0.0112 \times \text{SCR} \times 88.4-0.0124 \times \text{AGE}+0.339 \times \log(\text{AGE}-0.226))$

- **Cockcroft-Gault**
  - Male: $\text{eGFR (mL/min) = } (140-\text{AGE}) \times \text{WT}/(\text{SCR} \times 72)$
  - Female: $\text{eGFR (mL/min) = } (140-\text{AGE}) \times \text{WT}/(\text{SCR} \times 72) \times 0.85$

- **Simcyp default model**
  - $\text{eGFR (mL/min) = } (-6.616 \times \text{BSA}^2) + (99.054 \times \text{BSA}) - 17.74$

- **Rhodin model**
  - $\text{eGFR (L/hr) = } (\text{WT}/70)^{0.75}(\text{PMA}^{3.4}/(\text{PMA}^{3.4}+47.7^{3.4}))^{7.26}$

Maturation-based models for comparison
How Well Does eGFR Predict Gadobutrol CL?

Gadobutrol: renal elimination > 99% via glomerular filtration as unchanged drug. No plasma protein binding, no metabolism.

eGFR from equation of British Columbia Children’s Hospital shows low correlation with Gadobutrol CL.
How Well Does eGFR Predict Gadobutrol CL?

High Correlation ≠ Accurate Prediction
Overprediction of Gadobutrol CL by Schwartz Equation
How Well Does eGFR Predict Gadobutrol CL?

- eGFR from Leger and C-G equations over-predicts Gadobutrol CL by ~4 fold
- Schwartz equations over-predicts Gadobutrol CL by ~2 fold
Gadoterate: renal elimination > 99% via glomerular filtration as unchanged drug. No plasma protein binding, no metabolism.
Over-Estimating Drug Clearance Using Schwartz Equations

Schwartz equation adopted by FDA 2014 Clin Pharm Guidance: k=0.33 for LBW<1yr, 0.45 for Term <1 yr, 0.55 for >= 1 yr female, 0.70 for >= 1 yr male

Bedside Schwartz equation: k=0.413


https://www.fda.gov/media/90358/download
eGFR Calculated from Schwartz Equation Exceeds Upper Limit of Normal Range

Normal GFR in Children and Adolescents

<table>
<thead>
<tr>
<th>Age (Sex)</th>
<th>Mean GFR ± SD (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>2–8 wk (males and females)</td>
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<td>140 ± 30</td>
</tr>
<tr>
<td>13–21 y (females)</td>
<td>126 ± 22</td>
</tr>
</tbody>
</table>

Solid line: mean value of normal GFR
Dashed line: mean ± 2SD of normal GFR
Dots: eGFR calculated by Schwartz equation

eGFR(mL/min*1.73) = k*HT/SCR

Each color represents different data source of each drug
eGFR was calculated by Schwartz equations with k=0.33, 0.45, 0.55 and 0.70 (FDA Guidance)
<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Drug Name</th>
<th>Product Labeling</th>
<th>Age</th>
<th>Renal equations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-infection</td>
<td>Avycaz (ceftazidime and avibactam)</td>
<td>Dosage adjustment required if eGFR ≤ 50 mL/min/1.73 m²</td>
<td>≥ 2 y</td>
<td>k=0.413</td>
</tr>
<tr>
<td></td>
<td>Cefdinir</td>
<td>Lower dose is given to pediatric patients with CrCL &lt;30 mL/min/1.73m²</td>
<td>6 m – 12 y</td>
<td>k=0.55 for pediatric patients &gt;1 y/o, k=0.45 for &lt;=1y/o</td>
</tr>
<tr>
<td></td>
<td>Ceftaroline fosamil</td>
<td>CrCL &lt; 50 mL/min/1.73 m²: Insufficient information to recommend dose for peds.</td>
<td>&gt; 2 m</td>
<td>N/A</td>
</tr>
<tr>
<td>Partial-onset seizures</td>
<td>Lacosamide</td>
<td>For patients with CrCL &lt; 30 mL/min/1.73 m² or ESRD, a reduction of 25% of the maximum dosage is recommended.</td>
<td>4 - &lt;17 y</td>
<td>N/A</td>
</tr>
<tr>
<td>Chronic iron overload</td>
<td>Deferasirox</td>
<td>Do not use if baseline eGFR &lt; 40 mL/min/1.73m². Exercise caution if baseline eGFR is 40-60 mL/min/1.73m². Reduce the dose by 10 mg/ kg/day if eGFR decreases by &gt; 33%. Discontinue therapy for eGFR &lt; 40 mL/min/1.73m²</td>
<td>≥ 2 y</td>
<td>N/A</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Digoxin</td>
<td>Pediatric Patients Over 10 Years Old: Total Maintenance Dose = Loading Dose (i.e., Peak Body Stores) x % Daily Loss/100 (% Daily Loss = 14 + Creatinine clearance/5) Pediatric patients 5-10 y/o: average daily maintenance dose requirements is based on estimated CrCL.</td>
<td>&gt; 5 y</td>
<td>k=0.33 for preterm babies, 0.45 for term infants, 0.55 for pediatric patients and adolescent girls, 0.7 for adolescent boys</td>
</tr>
<tr>
<td>Anti-virus</td>
<td>Valganciclovir</td>
<td>Pediatric Dose (mg) = 7 x BSA x CrCL. Use the value of 150 if CrCL &gt; 150 mL/min/1.73 m²</td>
<td>1 m – 16 y</td>
<td>K=0.33 for LBW Infants &lt;1 y/o, k=0.45 for non-LBW Infants &lt;1 y/o, and 1 - &lt;2 y/o children, k=0.55 for boys 2 - &lt; 13 y/o and girls 2 - &lt; 16 y/o, k=0.7 for boys 13-16 y/o.</td>
</tr>
<tr>
<td>Angiography</td>
<td>Iopamidol, Iohexol, Ioversol</td>
<td>Pediatric pts with serum creatinine &gt; 1.5 mg/dL may have higher risk of adverse events</td>
<td>Varies from after birth to &gt; 2 y</td>
<td>N/A</td>
</tr>
<tr>
<td>Computed Tomography</td>
<td>Iopromide, Iodixanol</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Implications of Schwartz Equation for Dose Selection in Pediatric Patients: Case Example

Valcyte (valgancyclovir): A prodrug of ganciclovir, rapidly metabolized to ganciclovir, which is >90% renal eliminated through glomerular filtration and active tubular secretion

Pediatric dosage recommendation includes adjustment for renal impairment

![Equation: Pediatric Dose (mg) = \(7 \times BSA \times \text{CrCl}\) calculated using a modified Schwartz formula. If Schwartz creatinine clearance exceeds 130 mL/min/1.73m², then a maximum value of 150 mL/min/1.73m² should be used in the equation.

\[
\text{Masteller BSA (m²)} = \frac{\text{Height (cm)} \times \text{Weight (kg)}}{3600}
\]

\[
\text{Schwartz Creatinine Clearance (mL/min/1.73m²)} = \frac{k \times \text{Height (cm)}}{\text{Serum Creatinine (mg/dL)}}
\]

where \(k\) =
- 0.45 for patients aged 4 months to < 1 year,
- 0.45 for patients aged 1 to < 2 years (note \(k\) value is 0.45 instead of the typical value of 0.55),
- 0.55 for boys aged 2 to < 13 years and girls aged 2 to 16 years, and
- 0.7 for boys aged 13 to 16 years.

- Initial dosing recommendation did not include a maximum value for CrCl in children

FDA Safety Announcement on 09-15-2010\(^1\):

- Be aware of possible valganciclovir overdose in pediatric patients with low body weight, low body surface area, or below normal serum creatinine.
- When calculating the pediatric dose of Valcyte with the modified Schwartz formula, a maximum value of 150 mL/min/1.73 m² should be used in the formula.
- When the calculated pediatric dose of Valcyte exceeds 900 mg, a dose of 900 mg should be administered to the child.

\(^1\)http://www.fda.gov/Drugs/DrugSafety/ucm225727.htm
SCR-based Models in Drug Development

• BSA-adjusted eGFR correlates but is often higher than observed clearance of renally-eliminated drugs.

• eGFR calculated from Schwartz equation significantly exceeds upper limit of normal ranges, possible reasons include:
  – Assay variations
  – Biological variations

• Dose selection in pediatric patients with renal impairment
  – Requires actual pediatric patient data (possible overdosing using SCR-based prediction)
  – Serum creatinine data should be incorporated into population modeling
  – For drugs with altered dosage guidelines for adults with renal impairment, pediatric guidelines should be developed also
Renal Impairment in Pediatrics

**Challenges**

- Lack of markers for assessing renal impairment
- Lack of large PK, biomarker and clinical outcome data
- Lack of consensus, rationale on dosing strategies
- Lack of specific drug labels

**Opportunities**

- Identify new renal biomarkers for pediatric renal impairment
- Collect and share PK and clinical data to create large clinical database
- Optimize and standardize dosing strategies
- Enhance drug labels for neonates and infants.

*Collaboration between clinicians and scientists in academia, industry and regulatory agencies is the key.*

Adapted from Rodieux, Clinical pharmacokinetics, 2015
Summary

• Age based renal maturation models are used in population PK modeling for drugs that are primarily eliminated via renal pathway to inform initial dose selection for newborns and infants in clinical trials.

• SCR-based eGFR correlates but is often higher than observed clearance of renally-eliminated drugs.

• Different renal function models were built from different data sources, and significant differences exist between these models.

• More high-quality data are needed to support an optimal model, especially for pre-term infants and patients with renal impairment.

• However, we should start to apply what we know to current pediatric drug development.
List of References about Equations to Calculate eGFR

Acknowledgments

- FDA
  - Office of New Drugs, CDER
    - Lynne P. Yao
    - John Alexander
    - Yifei Zhang
    - Mona Khurana
    - Hari Sachs
    - Lesley Furlong
    - Charles J. Ganley
  - Office of Clinical Pharmacology, CDER
    - Gilbert Burckart
    - Yaning Wang
    - Shiew Mei Huang
    - Issam Zineh
  - Office of Pediatric Therapeutics
    - Gerri Baer
    - Suzie McCune
- University of Utah
  - Shaun S. Kumar
  - Catherine Sherwin
  - Bob Ward
- Children’s National Medical Center
  - John van den Anker
- NCTR
  - Jeff Fisher
  - Xiaoxia Yang
PBPK of Renally Cleared Drugs

Predictive Performance of Physiologically Based Pharmacokinetic and Population Pharmacokinetic Modeling of Renally Cleared Drugs in Children

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DOI 10.1007/s40262-016-0445-9

Physiologically Based Pharmacokinetic P and Emtricitabine in Neonates and Infant

Peng Duan¹ · Jeffrey W. Fisher² · Kenta Yoshida³ · Lei Zhang³ · Gilbert J. Burecart³ · Jian Wang³

Ontogeny of renal function captured in the Simcyp pediatric module was used in both studies
A Direct Comparison of All Models
Estimation of GFR

• Renal clearance
  – Equivalent volume of plasma from which a substance would have to be totally removed to account for its excretion in urine (per unit of time)

• Clearance of a substance can be used to estimate GFR if:
  – Substance is filtered to the same extent as water
  – Not reabsorbed or secreted by the tubule
  – Not metabolized or synthesized by the kidney
Comparison of Drug CL with eGFR

Amikacin

Vancomycin
The subjects who have abnormally high eGFR corresponds to low SCR measurement

X-axis: Age (Year), BMI, BSA (m²), CL (mL/min), Weight (kg), GA (weeks), Height (cm)
Y-axis: SCR (mg/dL)
Red dots: eGFR higher than mean + 2*SD of normal range
Blue dots: eGFR normal or low

Is the abnormally high eGFR just an artifact of SCR measurement error?
eGFR was calculated by Schwartz equations with k=0.33, 0.45, 0.55 and 0.70 (FDA Guidance)
Case study: Meropenem PK Highlights

- Administered as IV infusion in adults and children >3 months
- Protein binding is ~2%
- ~70% excreted unchanged by the kidneys
- Dosage adjustment is necessary in patients with creatinine clearance 50 mL/min or less
- $T_{1/2}$ ~1 hour

https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/050706s035lbl.pdf
Meropenem Dosing Regimen

1. Cohort 1: 20 mg/kg every 12 hours in infants <32 weeks GA and PNA <2 weeks
2. Cohort 2: 20 mg/kg every 8 hours in infants <32 weeks GA and PNA ≥2 weeks
3. Cohort 3: 20 mg/kg every 8 hours in infants ≥32 weeks GA and PNA <2 weeks
4. Cohort 4: 30 mg/kg every 8 hours in infants ≥32 weeks GA and PNA ≥2 weeks

✓ The rationale for dose selection was based on simulation studies performed from prior small meropenem PK studies in older infants.
✓ The simulation studies explored the likelihood of achieving a predefined therapeutic target by gestational and postnatal age.

Smith PB, Pediatric Infectious Disease Journal, 2011
Maturational changes in meropenem CL were included through covariates of PMA and Serum Creatinine in the final PopPK model.
Monte-Carlo Simulations were Used to Optimize the Dosing Regimen

Simulations demonstrated that the systemic concentrations remained:

- > 4 mcg/mL for 50% of the dose interval in 96% of patients;
- > 2 mcg/mL for 75% of the dose interval in 92% of patients.