Ontogeny of Renal Function: Applications 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
Renal Function and Glomerular Filtration Rate

- Normal Level of GFR Varies by Age

### 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>
<td>1 wk (males and females)</td>
<td>41 ± 15</td>
</tr>
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<td>2-8 wk (males and females)</td>
<td>66 ± 25</td>
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<td>&gt;8 wk (males and females)</td>
<td>96 ± 22</td>
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<td>2-12 y (males and females)</td>
<td>135 ± 27</td>
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<td>13-21 y (males)</td>
<td>140 ± 30</td>
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<tr>
<td>13-21 y (females)</td>
<td>126 ± 22</td>
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### 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>

Excretion = Filtration – Reabsorption + Secretion

Hogg et Al. *Pediatrics* 2003
Current Population PK Modeling Approach

• A review based on 101 articles reporting PopPK models from 23 renally eliminated drugs
• Intention: to separate the effects of body size, age and renal diseases on drug clearance

Note: $F_{\text{kidney}}$ accounts for deviation from normal kidney function, eg, due to inflammatory disease or drug-related nephrotoxicity.
Outline

• **Ontogeny of 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
Key physiological components

- **Body size**
  - WT

- **Ante-natal development**
  - GA
  - Post-natal maturation
    - PNA

- **Kidney function**
  - SCr

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

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

- **Maturation**
  \[ F_{\text{maturation}} = \frac{PMA_{\text{Hill}}^{\text{Hill}}}{TM50_{\text{Hill}}^{\text{Hill}} + PMA_{\text{Hill}}^{\text{Hill}}} \]

- **Kidney**
  \[ F_{\text{kidney}} = \frac{GFR_{\text{actual}}^{\text{PWR}}}{GFR_{\text{std}}^{\text{PWR}}} \]

Pre-term (GA < 37 weeks): TM50=35, Hill=4.7
Full-term (GA > 37 weeks): TM50=40, Hill=14.5
Human renal function maturation: a quantitative description using weight and postmenstrual age

Malin M. Rhodin · 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

Table 1 Summary of pooled data used in the study

<table>
<thead>
<tr>
<th>Characteristics of the study</th>
<th>Study 1</th>
<th>Study 2</th>
<th>Study 3</th>
<th>Study 4</th>
<th>Study 5</th>
<th>Study 6</th>
<th>Study 7</th>
<th>Study 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method</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>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>(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>(2–22.8 years)</td>
<td>(0.3–17)</td>
<td>(0.5–33)</td>
</tr>
<tr>
<td>Mean weight (range)</td>
<td>(22.5 kg)</td>
<td>(41.9 kg)</td>
<td>(10.8 kg)</td>
<td>(1.6 kg)</td>
<td>(1.5 kg)</td>
<td>(44.6 kg)</td>
<td>(40.1 kg)</td>
<td>(1.1 kg)</td>
</tr>
<tr>
<td>Mean GFR (range)</td>
<td>(107 ml/min)</td>
<td>(131 ml/min)</td>
<td>(122 ml/min)</td>
<td>(29 ml/min)</td>
<td>(25 ml/min)</td>
<td>(108 ml/min)</td>
<td>(120 ml/min)</td>
<td>(23 ml/min)</td>
</tr>
<tr>
<td>More than one observation/subject</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Pathology available</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

- Maturation function based on PMA
- No efforts were made to distinguish pre-term and full-term neonates
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>~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>
## 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 (23-41)</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 (23-41)</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>
Predictive Performance for Drug Clearance Using PMA based Model (1)
Predictive Performance for Drug Clearance Using PMA based Model (2)
Model Application in Drug Development

• Case Example:
  – Gadobenate dimeglumine; gadolinium-based contrast agent with ~95% renal elimination
  – Pharmacokinetic simulations based on the maturation model was 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:
  – PMA based sigmoidal Emax model, in combination with body weight-based scaling and kidney function assessment, can be used in population PK modeling for drugs that are primarily eliminated via renal pathway to inform initial dose selection for newborns and infants with normal renal function in clinical trials.

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

• Ontogeny of 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
Serum-Creatinine (SCR)-based equations for Estimation of GFR

- **Schwartz**
  - eGFR (mL/min/1.73m²) = k*HT (cm)/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**
  - eGFR (mL/min/1.73m²) = k*HT (cm)/SCR (mg/dL) (k=0.413)
- **Counahan-Barratt**
  - eGFR (mL/min/1.73m²) = k*HT (cm)/SCR (mg/dL) (k=0.43)
- **Flanders Metadata**
  - eGFR (mL/min/1.73m²) = (0.0414*log(AGE) + 0.3018) *HT/SCR
- **Leger**
  - eGFR (mL/min) = (56.7*WT+0.142*(HT^2))/(SCR*88.4)
- **British Columbia Children’s Hospital**
  - eGFR (mL/min/1.73m²) = exp(1.18+0.0016*WT+0.01*HT+149.5/(SCR*88.4)-2141/((SCR*88.4)^2))
- **Lund-Malmo**, applicable if SCr < 1.70 mg/dL
  - Male: eGFR (mL/min/1.73m²) = exp(4.62-0.0112*SCR*88.4-0.0124*AGE+0.339*log(AGE))
  - Female: eGFR (mL/min/1.73m²) = exp(4.62-0.0112*SCR*88.4-0.0124*AGE+0.339*log(AGE-0.226))
- **Cockcroft-Gault**
  - Male: eGFR (mL/min) = (140-AGE)*WT/(SCR*72)
  - Female: eGFR (mL/min) = (140-AGE)*WT/(SCR*72)*0.85
- **Simcyp default model**
  - eGFR (mL/min) = (-6.616*BSA^2) + (99.054*BSA) - 17.74
- **Rhodin model**
  - eGFR (L/hr) = (WT/70)^0.75*(PMA^3.4/(PMA^3.4+47.7^3.4))*7.26

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

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

- eGFR from Leger and C-G equations over-predicts Gadobutrol CL by ~4 folds
- Schwartz equations over-predicts Gadobutrol CL by ~2 folds
Gadoterate: renal elimination > 99% via glomerular filtration as unchanged drug. No plasma protein binding, no metabolism.
Comparison of Drug CL with eGFR Calculated by Schwartz Equation

Amikacin

Vancomycin
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)

(k=0.413)
eGFR Calculated from Schwartz Equation
Exceeds Upper Limit of Normal Range

Normal GFR in Children and Adolescents

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</tr>
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</table>

Solid line: mean value of normal GFR
Dashed line: mean ± 2SD of normal GFR
Dots: eGFR calculated by Schwartz equation
\[ eGFR(\text{mL/min} \times 1.73) = k \times \frac{HT}{SCR} \]
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)
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

FDA Safety Announcement on 09-15-2010:

- 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.

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

\[
\text{Pediatric Dose (mg)} = 7 \times \left( \frac{\text{Height (cm)} \times \text{Weight (kg)}}{3600} \right) \times \text{CrCl (mL/min/1.73 m²)}
\]

```markdown
\[
\begin{align*}
\text{BSA (m²)} &= \sqrt{\frac{\text{Height (cm)} \times \text{Weight (kg)}}{3600}} \\
\text{Schwartz Creatinine Clearance (mL/min/1.73 m²)} &= \frac{k \times \text{Height (cm)}}{\text{Serum Creatinine (mg/dL)} \times 1.73 m²}
\end{align*}
\]

where

- 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.

Adapted from slides “Dose Adjustments for Renal Impairment in Pediatric Patients” by Fenan Solomon, Dec 2014

Application of SCR-based Models in Drug Development

- BSA-adjusted eGFR correlates but often higher than observed CL of predominantly renal-eliminated drugs

- eGFR calculated from Schwartz equation significantly exceeds upper limit of normal range, possible reasons include
  - Variations of SCR measurement at low concentration
  - Sub-optimal k values in Schwartz equation which varies by age

- Implications for pediatric dose selection
  - Selecting dose for initial clinical trial in pediatric patients
    - Potential use of eGFR to predict drug CL and dose for predominantly renal-eliminated drugs
  - Approval of dose for labeling
    - Establish an drug-specific equation based on observed data and pop-PK
    - Apply a upper limit on eGFR if using it to calculate dose
    - More data is needed to study dosing in renal-impaired pediatric patients
A Direct Comparison of All Models
Use of Pediatric Renal Function in Drug Development - Current Status

• For drugs with altered dosage guidelines for adults with renal impairment, pediatric guidelines should be developed also.
  – Requires some actual pediatric patient data, but M&S may be able to extend those dosage guidelines
  – Serum creatinine and some appropriate model should be acceptable for now
  – Additional experience may allow us to make better predictions in premature infants in the future
Summary

• Different renal function models were built from different data sources

• Significant differences exist between these models

• More high-quality data are needed to support an optimal model

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

Acknowledgments

• FDA
  – Yaning Wang
  – Yifei Zhang
  – Mona Khurana
  – Yu Jiang
  – Gilbert Burckart
  – Lynne P. Yao
  – Charles J. Ganley

• University of Utah
  – Shaun S. Kumar
  – Catherine Sherwin
  – Bob Ward
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)
eGFR calculated from Schwartz equation exceeds upper limit of normal range

Comparison of eGFR_Schwartz with normal range of GFR

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=0.413