Drug Prescribing in Kidney Disease: Initiative for Improved Dosing

Patient assessment for drug dosing

Section Leaders:
Stuart Goldstein and Frieder Keller
9:30 – 10:00 am

2) Patient assessment for drug dosing
Presenter: Stuart Goldstein and Frieder Keller

- Focusing on specific therapy
- Estimating extra-cellular fluid volume
- Estimating kidney function
- Determining other organ function
- Effects of the aging kidney on drug therapy
Preliminary Keywords

- Estimating kidney function
  MDRD GFR, CKD-EPI GFR, Cockcroft & Gault applicability in CKD versus AKI and CRRT
- Estimating extra-cellular fluid volume e.g. overhydration in the intensive care setting …
- Effects of the aging kidney on drug therapy
- determining other organ function e.g. liver impairment, frailty, co-morbidity …
- Frequent problems: anti-diabetic, anti-infective and anti-cancer drugs
- Potentially dangerous drugs: methotrexate, enoxaparin, lithium, metformin, cefepime
Prediction of creatinine clearance from serum creatinine.
Cockcroft DW, Gault MH. Nephron. 1976;16(1):31-41

\[ Cl_{\text{Crea}} = \frac{U \times V}{P} \]

\[
GFR = \frac{140 - \text{Age(years)}}{0.82 \times \text{Screa(\mu mol/L)} \cdot \text{Weight(kg)} \cdot 0.85(\text{female})}
\]

Serum Creatinine mg/dL x 88.4 = \(\mu\text{mol/L}\)
Use of the MDRD Study Equation to Estimate Kidney Function for Drug Dosing
L A Stevens, A S Levey
Clinical Pharmacology & Therapeutics 86, 465-467

Figure 1: Timeline of creatinine assay development, standardization procedures, and development of glomerular filtration rate estimating equations. IDMS refers to a program initiated by the National Kidney Disease Education Program to establish traceability of the creatinine assay to an isotope-dilution mass spectrometry reference measurement procedure calibrated using a pure crystalline creatinine primary standard from the National Institute for Standards and Technology. CKD-EPI, chronic kidney disease epidemiology collaboration; MDRD, Modification of Diet in Renal Disease.
Original 4-variable MDRD GFR mL/min per 1.73 m^2 BSA

\[ GFR = 186.3 \times \text{Scr}^{-1.154} \times \text{age}^{-0.203} \times 1.212 \times \begin{cases} 1 & \text{if black} \\ 0.742 & \text{if female} \end{cases} \]

Standardized serum creatinine (mg/dL) re-expressed MDRD GFR mL/min per 1.73 m^2 BSA

\[ \text{GFR} = 175 \times \text{stScr}^{-1.154} \times \text{age}^{-0.203} \times 1.212 \times \begin{cases} 1 & \text{if black} \\ 0.742 & \text{if female} \end{cases} \]

\[ 186.3 \times (1.0 / 0.95)^{-1.154} = 175.6 \]

Problem => individual BSA
Continuing the use of the Cockcroft-Gault equation for drug dosing in patients with impaired renal function.

Spruill WJ, Wade WE, Cobb HH 3rd.

This same procedure could be carried out using the C-G equation by also multiplying the resultant creatinine value by 0.95 to be “re-expressed” as

$$\frac{(140 - \text{age}) \times \text{weight}}{([\text{s.c.} \times 0.95] \times 72)} = 68 \times \text{serum creatinine}$$
The CKD-EPI equation, expressed as a single equation, is

\[
GFR = 141 \times \min(\text{Scr}/\kappa, 1)^{\alpha} \times \max(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018 \ [\text{if female}] \times 1.159 \ [\text{if black}]
\]

where Scr is serum creatinine, \( \kappa \) is 0.7 for females and 0.9 for males, \( \alpha \) is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/\( \kappa \) or 1, and max indicates the maximum of Scr/\( \kappa \) or 1.
An easy to calculate equation to estimate GFR based on inulin clearance.

Table 3. The GFR-adapted Cockcroft–Gault-like IB-eGFR equation

Newly fitted equation with exact constants (exact equation):
\[
GFR \ [\text{mL/min}] = (154.6999 - \text{Age} \ [\text{years}]) \times \text{weight} \ [\text{kg}] / \text{serum creatinine} \ [\mu\text{mol/L}] \times 0.8349 \text{ if female}
\]

Newly fitted equation with rounded constants (IB-eGFR):
\[
GFR \ [\text{mL/min}] = (155 - \text{Age} \ [\text{years}]) \times \text{weight} \ [\text{kg}] / \text{serum creatinine} \ [\mu\text{mol/L}] \times 0.85 \text{ if female}
\]

Tsinalis C&G equation

Tsinalis C&G equation

Kidney Disease: Improving Global Outcomes
A Comparison of GFR estimating formulae based upon s-cystatin C and s-creatinine and a combination of the two.

Tidman M, Sjöström P, Jones I.

\[ GFR = \frac{100}{CystatinC} - 14 \]
New Equations to Estimate GFR in Children with CKD

George J. Schwartz,* Alvaro Muñoz,† Michael F. Schneider,‡ Robert H. Mak,‡ Frederick Kaskel,§ Bradley A. Warady,‖ and Susan L. Furth††

\[
eGFR = 39.1 \left[ \frac{\text{height}}{\text{Scr}} \right]^{0.516} \left[ \frac{1.8}{\text{cystatin C}} \right]^{0.294} \times \left[ \frac{30}{\text{BUN}} \right]^{0.169} \left[ 1.099 \right]^{\text{male}} \left[ \frac{\text{height}}{1.4} \right]^{0.188},
\]

Yields 88% and 47% of eGFR within 30%,10% iGFR

\[
eGFR = 0.413 \left[ \frac{\text{height}}{\text{Scr}} \right],
\]

Yields 79% of eGFR within 30% of iGFR

Kidney Disease: Improving Global Outcomes

www.kdigo.org
AKI + ICU + CRRT

MDRD-2 GFR = 186 \times [SCrea]^{1.154} \times [Age]^{0.203}

Kidney Disease: Improving Global Outcomes
Antimicrobial dosing strategies in critically ill patients with acute kidney injury and high-dose continuous veno-venous hemofiltration

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Current Opinion in Critical Care 2008, 14:664–659

Purpose of review
Delivery of appropriate antimicrobial therapy is a great challenge during continuous veno-venous hemofiltration (CVVH), particularly if the recommended higher doses are applied. The present contribution discusses the principles of drug dosing during CVVH and compares the various proposed dosing strategies.

Recent findings
The basic principles underlying removal of antibiotics during CVVH and the published dosing strategies are reviewed. The key factor to consider is the fractional CVVH clearance ($Fr_{CVVH}$). Critical illness and acute kidney injury, however, may dramatically affect the pharmacokinetic properties of a drug and thus $Fr_{CVVH}$. Five dosing strategies have been proposed on the basis of either available references, total creatinine clearance, the reduction in total body clearance, the maintenance dose multiplication factor, or therapeutic drug monitoring. Dose predictions according to the various strategies show reasonable approximations for some but not all antibiotics.

Jelliffe equation for unstable kidney function:

\[(\text{Volume of distribution} \times (\text{sCr on day1} - \text{sCr on day2})) + \text{creatinine production}) \times 100/1440/\text{average sCr}].

\[
\text{Creatinine production (mg/day)} = [29.305 - (0.203 \times \text{age})] \times \text{weight} \times [1.037 - (0.0338 \times \text{average Cr})] \times \text{correction for gender (0.85 for males and 0.765 for females)}.
\]

\[
\text{Adjusted Cr} = \text{sCr} \times \left[ \frac{\text{hospital admission WT (kg)} \times 0.6 + (\text{daily fluid balance})}{\text{hospital admission weight}} \right] \times 0.6.
\]
Conclusion

Assessment of kidney function by
• Classical Cockcroft & Gault CLcrea equation
• Classical MDRD-2 eGFR equation
• IDMS crea MDRD eGFR equation
• CKD EPI eGFR formula
• Tsinalis simplified C&G GFR equation
• Jelliffe modified

Could equally be used – depending on local experience, availability
## Volume and fluid overload in the ICU

<table>
<thead>
<tr>
<th></th>
<th>Shock (n=49)</th>
<th>No shock (n=60)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg/kg)</td>
<td>6.3 (0.8)</td>
<td>6.1 (1.1)</td>
<td>0.2</td>
</tr>
<tr>
<td>CLcreat (ml/min)</td>
<td>79 (19)</td>
<td>83 (24)</td>
<td>0.3</td>
</tr>
<tr>
<td>Cmax (mg/l)</td>
<td>18.5 (5.6)</td>
<td>21.3 (7.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>CL (ml/min)</td>
<td>80 (35)</td>
<td>85 (43)</td>
<td>0.5</td>
</tr>
<tr>
<td>Vd (ml/kg)</td>
<td>353 (128)</td>
<td>287 (100)</td>
<td>0.004</td>
</tr>
<tr>
<td>Kel (h⁻¹)</td>
<td>0.19 (0.07)</td>
<td>0.24 (0.11)</td>
<td>0.01</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>4.3 (2)</td>
<td>3.7 (1.9)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Buijk SE, Mouton JW, Gyssens IC, Verbrugh HA, Bruining HA.
Experience with a once-daily dosing program of aminoglycosides in critically ill patients.
Drug Dose: Liver Function and Physical Function

Child Pugh score

MELD score (> 20 = liver failure ) =
  +3.8×ln [bilirubin (mg/dl)]
  +11.2×ln [INR]
  +9.6×ln [creatinine(mg/dl)]
  +6.4×(etiology: 0 if cholestatic or alcoholic, 1 otherwise)

Karnofsky performance score
  70% weakness
  40% bed-bound

Frailty ? Co-Morbidity ?
... assessing both, the patient and the drug

- Therapeutic Drug Monitoring
  peak concentration
  trough concentration
  target concentration
  plasma binding

- Pharmacogenetics, Pharmacogenomics
  fast metabolizer
  slow metabolizer
Pharmacokinetics and Age

N = 137 Drugs

Review on pharmacokinetics and pharmacodynamics and the aging kidney.
Aymanns C, Keller F, Maus S, Hartmann B, Czock D
Assessment of Organ Function

- Chronic Kidney Disease
- Acute Kidney Injury
- Intensive Care Unit
- Continuous Renal Replacement Therapy
- Liver Failure
- Frailty
- Age