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

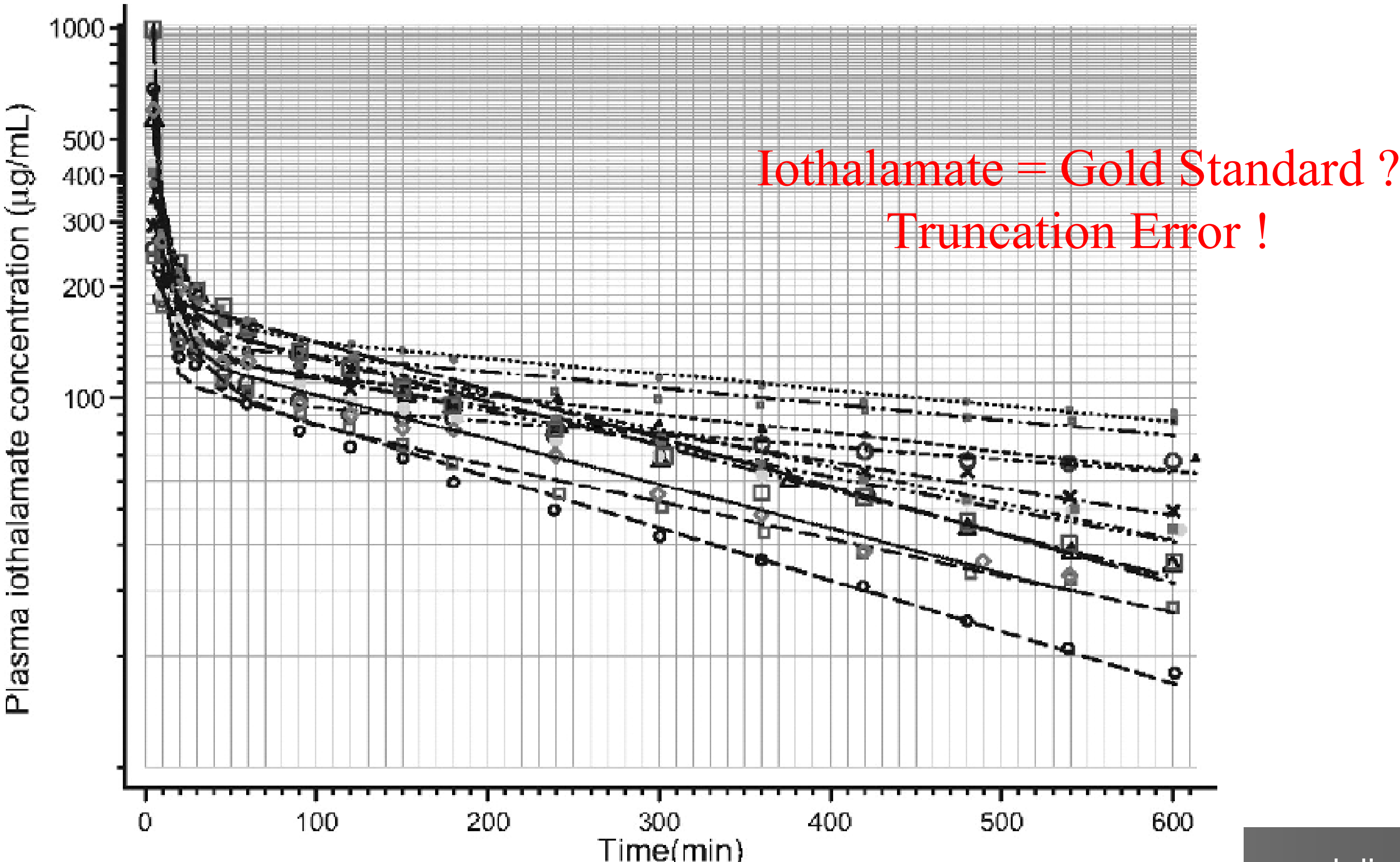
- Estimating kidney function
  MDRD GFR, CKD-EPI GFR, Cockcroft & Gault
  applicability in CKD versus AKI and CRRT
- Estimating extra-cellular fluid volume e.g. overhydration in the intensive care setting …
- Effects of the aging kidney on drug therapy
- determining other organ function e.g. liver impairment, frailty, co-morbidity …

- Frequent problems: anti-diabetic, anti-infective and anti-cancer drugs
- Potentially dangerous drugs: methotrexate, enoxaparin, lithium, metformin, cefepime

Clin J Am Soc Nephrol. 2009 Jan;4(1):77-85. Epub 2008 Nov 12.

Assessment of iothalamate plasma clearance: duration of study affects quality of GFR.

Agarwal R, Bills JE, Yigazu PM, Abraham T, Gizaw AB, Light RP, Bekele DM, Tegegne GG.



Prediction of creatinine clearance from serum creatinine.

Cockcroft DW, Gault MH.

Nephron. 1976;16(1):31-41

ClCrea = U x V / P

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

Serum Creatinine mg/dL x 88.4 = µmol/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

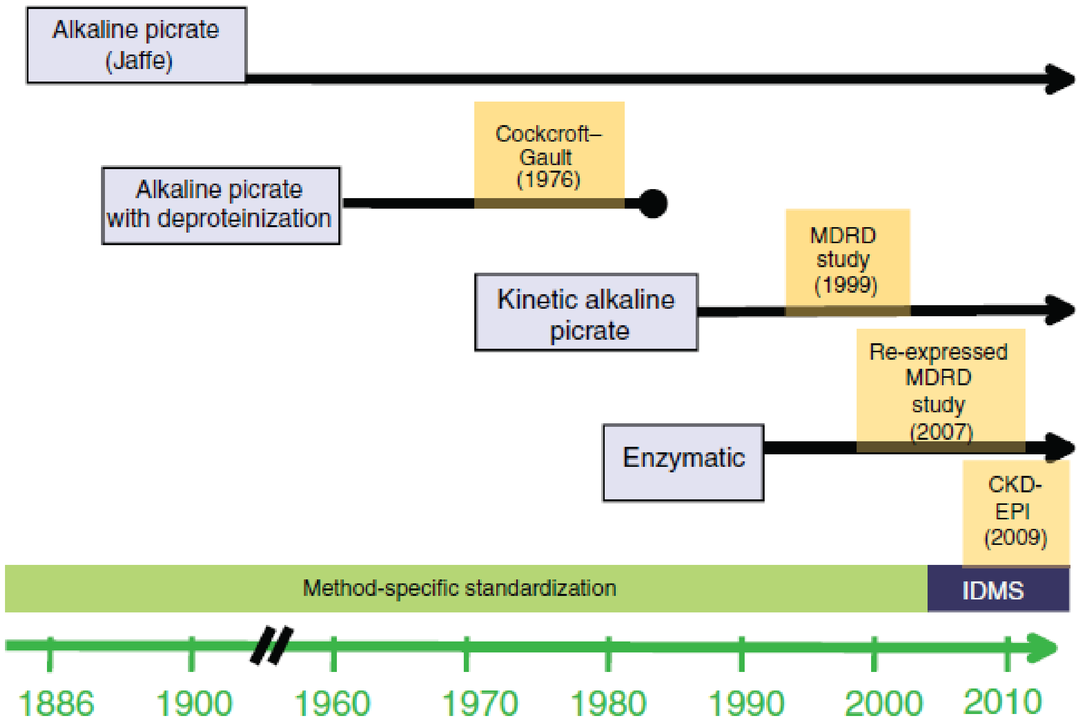


Figure 1 Timeline of creatinine assay development, standardization procedures, and development of glomeruler filtration rate estimating equations. IDMS refers to a program initiated by the National Kidney Disease Education Program to establish traceability of the creatinine assay to an isotope-dilution 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.

Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F; Chronic Kidney Disease Epidemiology Collaboration.
Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate.
Ann Intern Med. 2006 Aug 15;145(4):247-54.

Original 4-variable MDRD GFR mL/min per 1.73 m^2 BSA

GFR = 186.3 x Scr^-1.154 x age^-0.203 x 1.212 [if black] x 0.742 [if female]

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

GFR = 175 x stScr^-1.154 x age^-0.203 x 1.212 [if black] x 0.742 [if female]

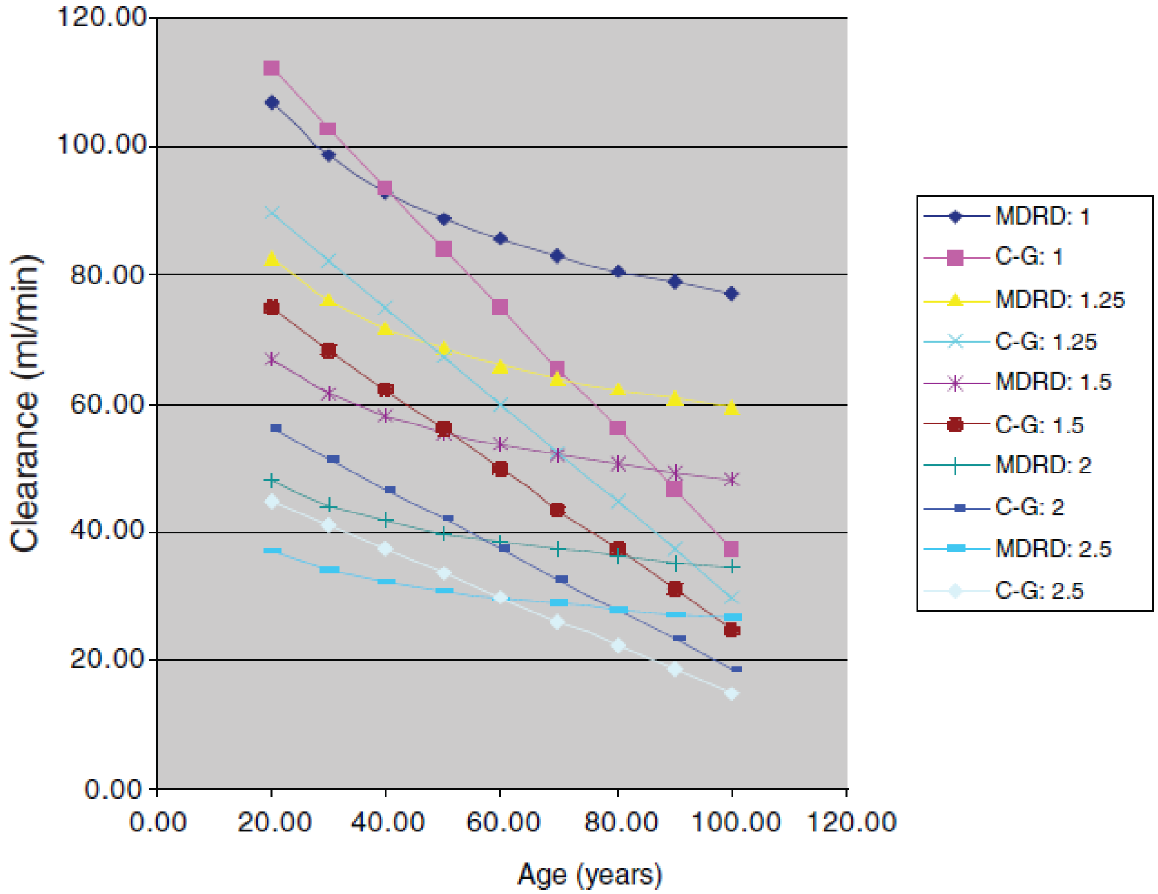
186.3*(1.0 / 0.95)^-1.154 = 175.6

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.

Clin Pharmacol Ther. 2009 Nov;86(5):468-70.



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

[(140 – age) × weight] / [((s.c. x 0.95) × 72 =) 68 × serum creatinine]

Ann Intern Med. 2009 May 5;150(9):604-12.

A new equation to estimate glomerular filtration rate.

Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration).

The CKD-EPI Equation for Estimating GFR on the Natural Scale*

Race and Sex	Serum Creatinine µmol/L (mg/dL)	Equation
Black		
Female	≤62 (≤0.7)	$GFR = 166 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 166 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 163 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 163 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$
White or other		
Female	≤62 (≤0.7)	$GFR = 144 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 144 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 141 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 141 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$

The CKD-EPI equation, expressed as a single equation, is

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

where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

Tsinalis D, Thiel GT.
Nephrol Dial Transplant. 2009 Oct;24(10):3055-61. Epub 2009 Apr 25.
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 [mL/min] = (154.6999 − Age [years]) × weight [kg]/serum creatinine [μmol/L]] × 0.8349 if female

Newly fitted equation with rounded constants (IB-eGFR):
GFR [mL/min] = (155 − Age [years]) × weight [kg]/serum creatinine [μmol/L]] × 0.85 if female

Tsinalis C&G equation`=> advantage: BW not BSA, less coefficients

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.

Nephrol Dial Transplant. 2008 Jan;23(1):154-60.

$$GFR = \frac{100}{CystatinC} - 14$$

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[†¶]

J Am Soc Nephrol 20: 629–637, 2009

$$eGFR = 39.1[height/Scr]^{0.516}[1.8/cystatin\ C]^{0.294}$$

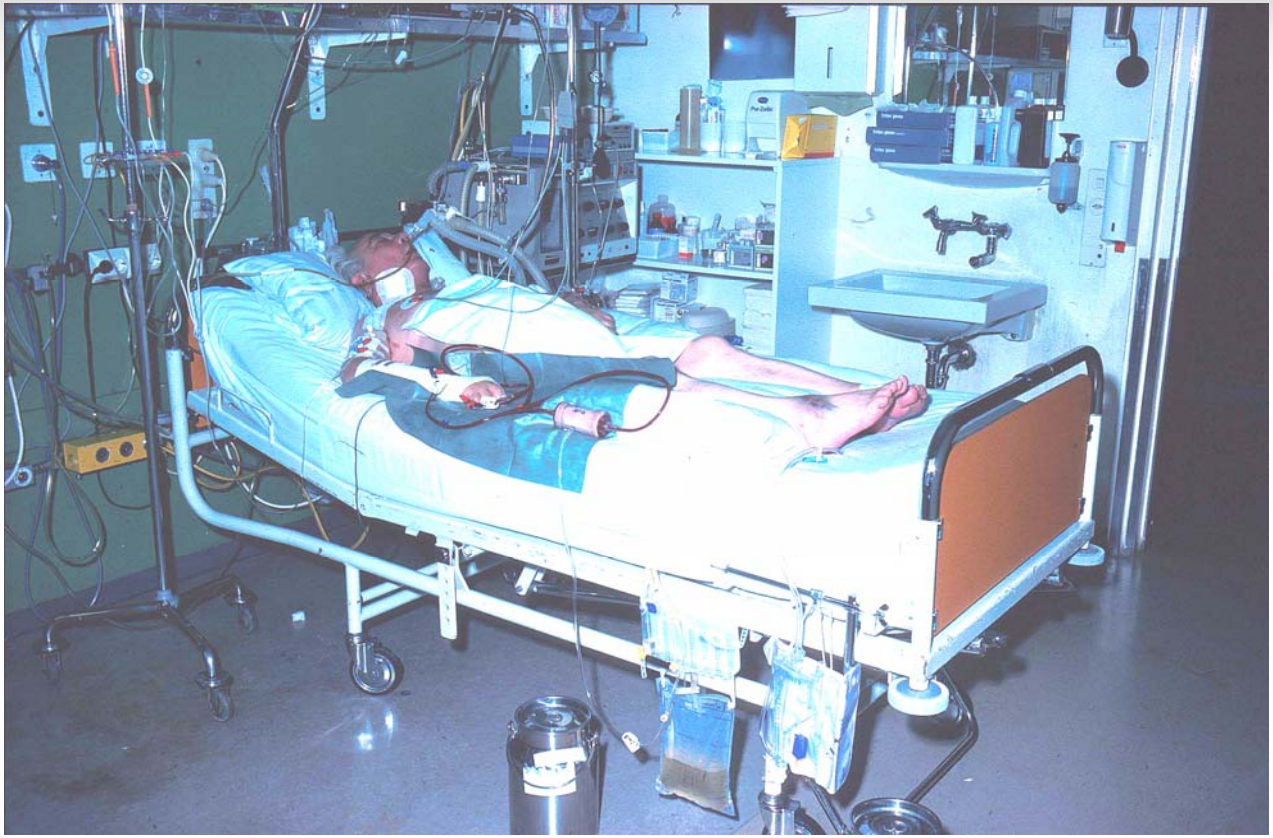
$$\times [30/BUN]^{0.169}[1.099]^{male}[height/1.4]^{0.188},$$

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

$$eGFR = 0.413[height/Scr],$$

Yields 79% of eGFR within 30% of iGFR

AKI + ICU + CRRT



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

ICU & CRRT

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, 14:654–659

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

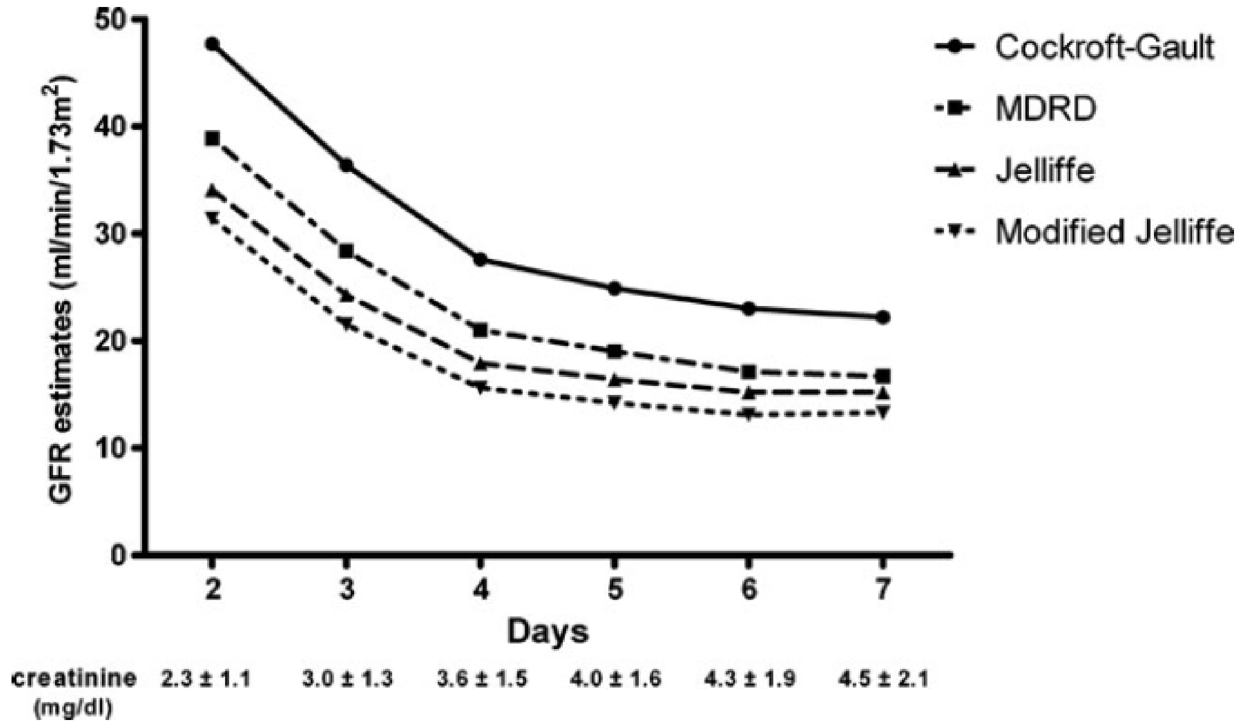
The basic principles underlying removal of antibiotics during CVVH and the published dosing strategies are reviewed. The key factor to consider is the fractional CVVH clearance (Fr_{CVVH}). Critical illness and acute kidney injury, however, may dramatically affect the pharmacokinetic properties of a 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.

Kidney Disease: Improving Global Outcomes

Bouchard J, Macedo E, Soroko S, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP, Mehta RL; Program to Improve Care in Acute Renal Disease.

Nephrol Dial Transplant. 2010 Jan;25(1):102-7. Epub 2009 Aug 13.

Comparison of methods for estimating glomerular filtration rate in critically ill patients with acute kidney injury.



Jelliffe equation for unstable kidney function

•((Volume of distribution × (sCr on day1 − sCr on day2)) + creatinine production) × 100/1440/average sCr.

•Creatinine production (mg/day) = [29.305 − (0.203 × age)] × weight × [1.037 − (0.0338 × average Cr)] × correction for gender (0.85 for males and 0.765 for females).

•Adjusted Cr = sCr × [hospital admission WT (kg) ×0.6 + (daily fluid balance)]/hospital admission weight × 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

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

Buijk SE, Mouton JW, Gyssens IC, Verbrugh HA, Bruining HA.
Experience with a once-daily dosing program of aminoglycosides in critically ill patients.
Intensive Care Med. 2002 Jul;28(7):936-42.

Drug Dose: Liver Function and Physical Function

Child Pugh score

=> limitations (Verbeeck RK. Eur J Clin Pharmacol 2008,64:1147-61)

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

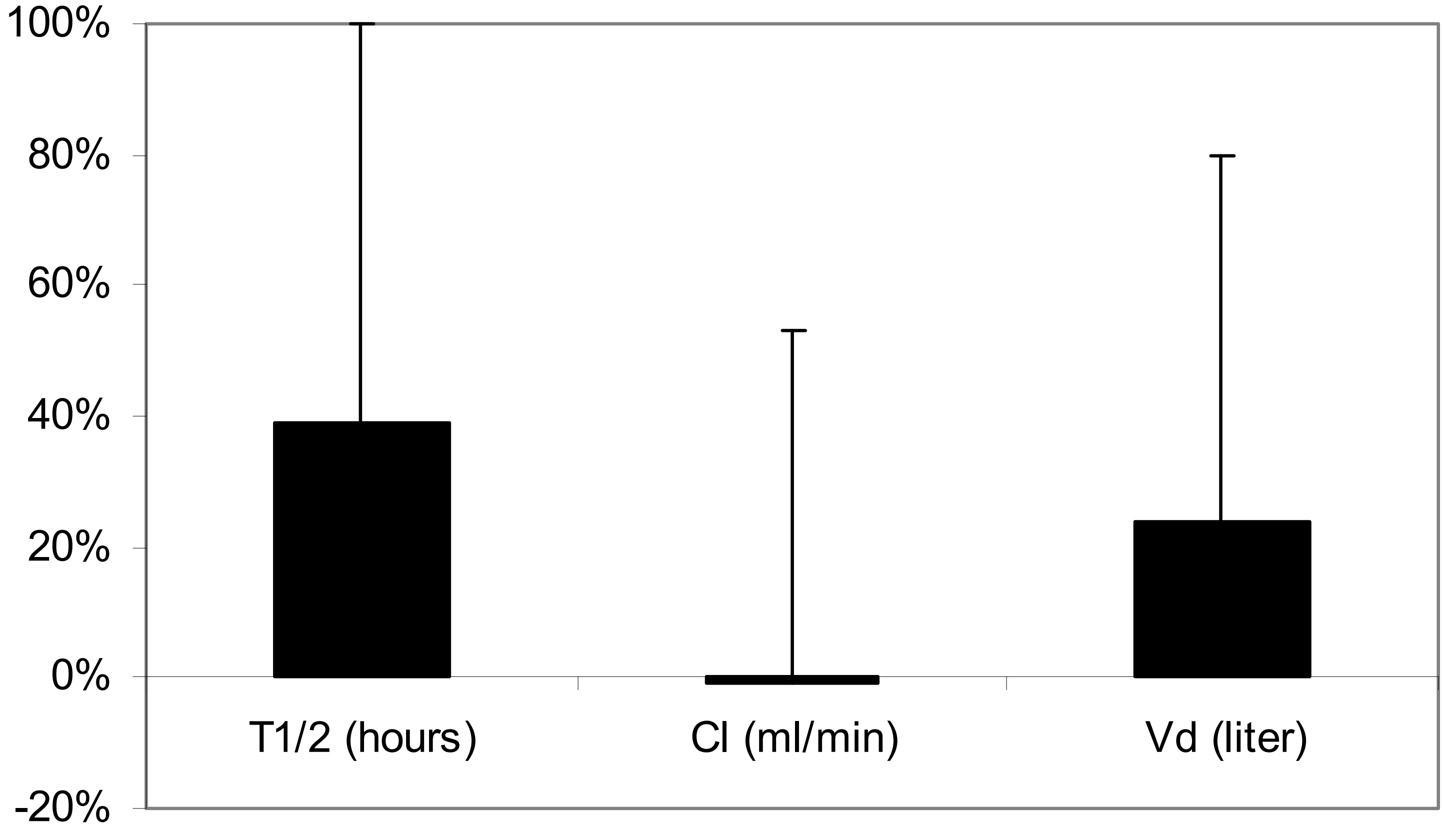
Frailty ? Co-Morbidity ?

… 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



Clin J Am Soc Nephrol. 2010 Feb;5(2):314-27.

Review on pharmacokinetics and pharmacodynamics and the aging kidney.

Aymanns C, Keller F, Maus S, Hartmann B, Czock D

Assessmant of Organ Function

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