Drug Prescribing in Kidney Disease: Initiative for Improved Dosing

Calculating Drug Doses in AKI

Section Leaders:

Brian Decker and Deborah Pasko

Overview of AKI

- Mostly affects critically ill patients
- High mortality despite great advances
- Still controversy over clearance equations

AKI and Pharmacokinetics

- Absorption, Distribution, Metabolism, Excretion (Elimination)
- Absorption: GI changes, drugs, nutrition, bacterial overgrowth
- Distribution – most complicated but needs the most attention
- Metabolism – Discussed later
- Elimination – what to do?

Distribution

- Numerous fluid overload studies (adults and peds)
- Need to balance hydration for kidney perfusion vs. total body fluid overload
- Fluid restriction, diuretics, RRT
- Drugs most impacted are small Vd (AG's, vanco, Pb, most atb)

Fluid and AG example

- 8.5kg child receives a gent dose of 21mg (2.5mg/kg)
- What peak concentration (mg/L) can be expected?
- Volume of distribution of gent is 0.2-0.4L/kg
- 0.25L/kg is normal, but in fluid overloaded patients, expect higher values. If 0.3L/kg =
  - 2.55 Liters = Vd
  - 21mg/2.55L = 8.2 mg/L assuming no drug removal (and constant kel)

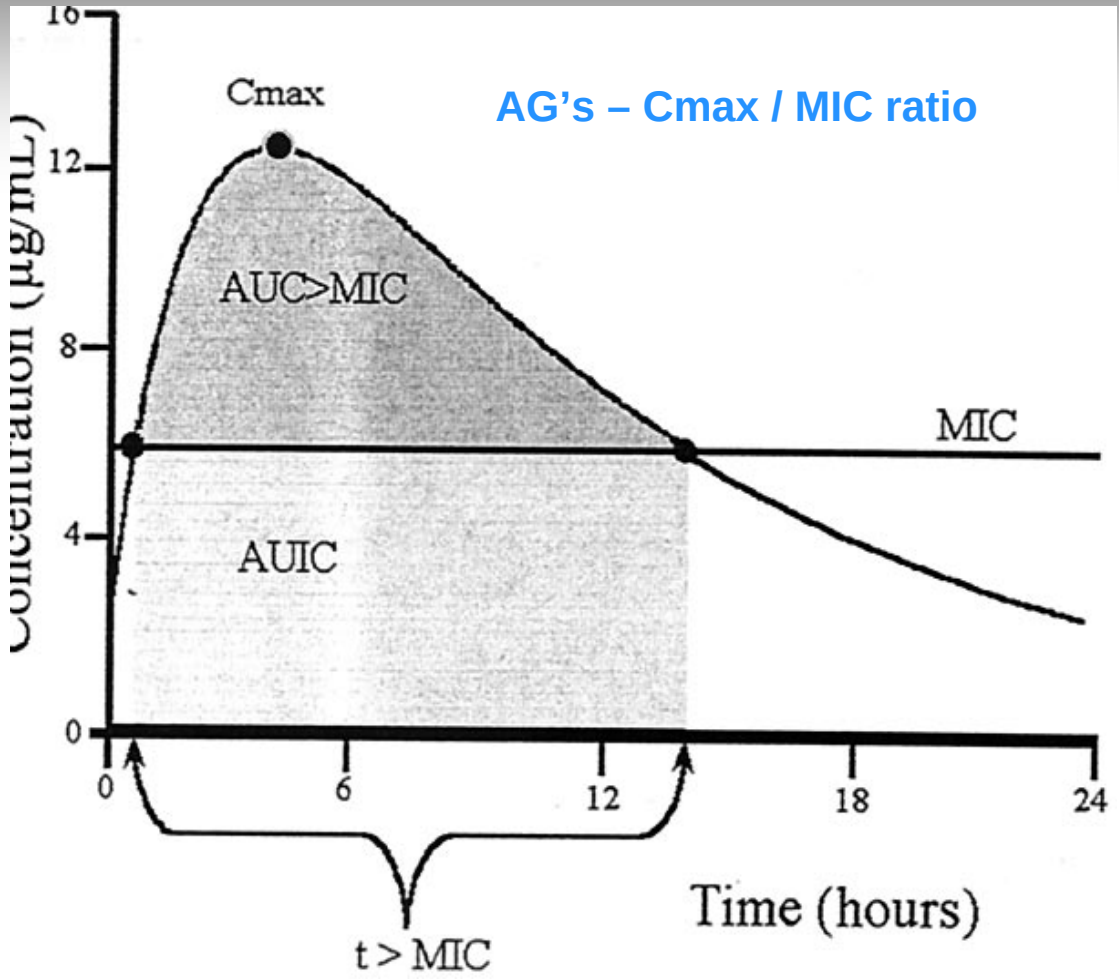
AG example

30 min after the 21mg dose is done a peak is done = 4.0mg/L

What is the patients actual volume of distribution?

5.1 Liters = 0.6L/kg

(compare to normal values!!!!)



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 2004, p. 369–377 Vol. 48, No. 2

More distribution

- Critical care considerations
  - Acid base status – pH dependent drugs (nicardipine, atracurium)
  - Acute phase responses – A1G (lidocaine)
  - Uremia (phenytoin)
  - Albumin replacements
  - Advanced technology: CRRT, ECMO, MARS
    - Binding of proteins on membranes
    - Binding of proteins on tubing

Elimination

- Cockcroft-Gault
- MDRD
- Schwartz equation
- Which one in AKI?

Elimination: RIFLE and pRIFLE

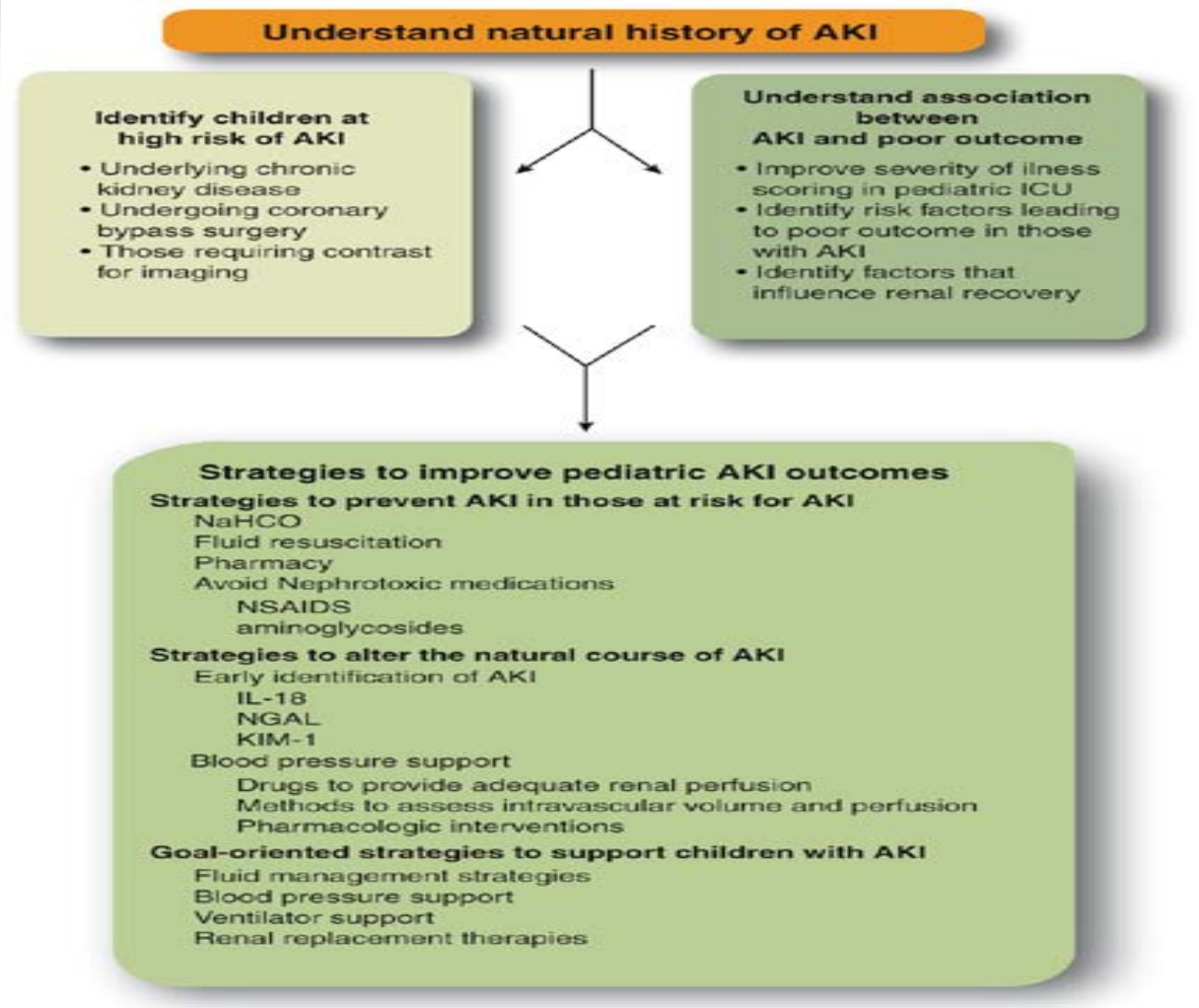
Adult					Pediatric		
AKIN		AKIN/RIFLE	RIFLE		pRIFLE		
Stage	Serum Cr	Urine output	Class	Serum Cr or GFR	Class	eCCl by Schwartz formula	Urine output
I	↑SCr >0.3 mg/dl or ↑SCr >150.200% from baseline	<0.5 ml/kg per hour≈6 h	Risk	↑SCr by 150% or GFR decrease by 25%	Risk	eCCl decrease by 25%	<0.5 ml/kg per hour≈8 h
II	↑SCr to >200-300% from baseline	<0.5 ml/kg per hour >12 h	Injury	↑SCr by 200% or GFR decrease by 50%	Injury	eCCl decrease by 50%	<0.5 ml/kg per hour≈16 h
III	↑SCr of >300% from baseline or SCr > 4.0 mg/dl with an acute rise of at least 0.5 mg/dl	<0.3 ml/kg per hour >24 h or anuria for >12 h	Fail	↑SCr by 300% or SCr > 4.0 mg/dl with acute rise of 0.5 mg/dl or GFR decrease by >75%	Fail	eCCl decrease by 75% or <35 ml/min per 1.73 m2 body surface area	<0.3 ml/kg per hour for 24 h or anuric for 12 h
			Loss	Failure > 4 weeks	Loss	Failure > 4 weeks	
			ESRD	Failure >3 months	ESRD	Failure >3 months	

Kidney Disease: Improving Global Outcomes

Askenazi DG, et al. Pediatr Nephrology 2009;24:265-274

www.kdigo.org

Drug Dosing and AKI: how to approach



Kidney Disease: Improving Global Outcomes

Askenazi DG, Bunchman TE. Kidney International (2007) ***71, 963–964. doi:10.1038/sj.ki.5002238***

Research Recommendations

- AKI dosing based on RIFLE criteria
- Proactive approach using RIFLE/pRIFLE, and biomarkers
- More research on non-renal clearance in AKI: CL(body) = CL(renal) + CL(hepatic) + CL(pulmonary) + CL(etc)

Drug Prescribing in Kidney Disease: Initiative for Improved Dosing

Calculating Drug Doses in AKI: Impact of non-renal clearance

Section Leaders:

Brian Decker and Deborah Pasko

Kidney Disease: Improving Global Outcomes

Calculating drug doses in AKI: impact of non-renal clearance

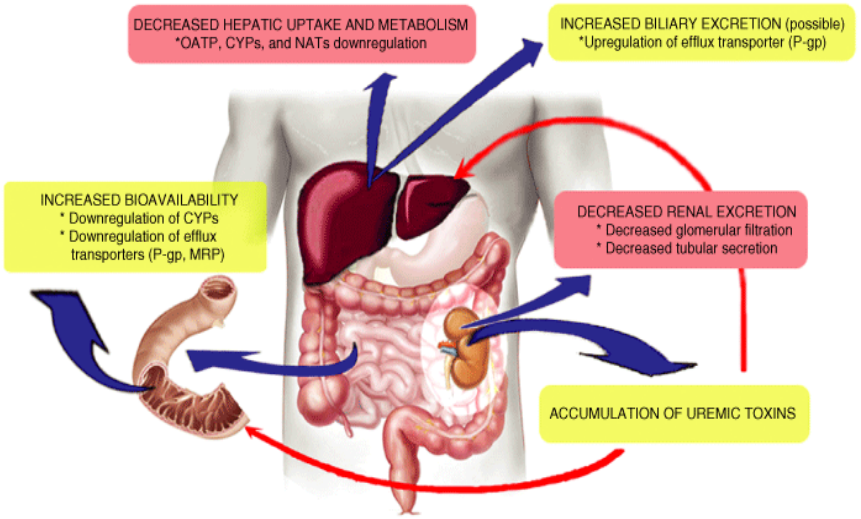
Objectives

- Background
- AKI and CYP450-mediated metabolism
- AKI and drug transport
- Renal replacement therapy and non-renal clearance
- Drug dosing recommendations
- Future research directions

Calculating drug doses in AKI: impact of non-renal clearance

Background

- Animal and human studies have shown that CYP450-mediated drug metabolism and drug transport is reduced in CKD and ESRD
- Postulated to be secondary to accumulation of inhibitory uremic solutes
- Inhibition of these metabolic processes may affect drug disposition leading to increased risk of drug toxicity
- Current AKI literature is conflicted with a majority of animal studies showing no effect on CYP450-mediated metabolism and human AKI studies showing decrements in nonrenal clearance



Nolin TD et al. Clin Pharmacol Therap, 2008.

AKI and CYP450-mediated metabolism

Drug	Animal	AKI model	Effect of AKI on hepatic metabolism
Clarithromycin	rat	Uranyl nitrate	⟷
Cyclosporine	rat	Gentamicin	⟷
Diltiazem	rat	Uranyl nitrate	↑
Diltiazem	rabbit	Folate	↓
Etoposide	rat	Uranyl nitrate	⟷
Losartan	rat	Uranyl nitrate and bilateral ureter ligation	⟷
Metoprolol	rat	Bilateral ureter ligation	⟷
Metoprolol	rat	Glycerol	⟷
Propranolol	rat	Cisplatin	⟷
Propranolol	rat	Bilateral ureter ligation	⟷
Tacrolimus	rat	Cisplatin	↓
Telithromycin	rat	Uranyl nitrate	⟷
Theophylline	rat	Uranyl nitrate	↑
Ajmaline	rat	Uranyl nitrate	⟷

- **Unlike CKD, most studies showed no effect from AKI on hepatic metabolism**
- **Others demonstrated increase or decrease in hepatic metabolism**
  - **Interspecies differences also observed**

Kidney Disease: Improving Global Outcomes

Adapted from Vilay AM et al. Critical Care,2008.

AKI and CYP450-mediated metabolism

- **Similarly, most studies did not show any effect from AKI on the metabolic activity of specific CYP450 enzymes**
- **Others showed an increase or decrease in CYP450 activity depending on AKI model used**
  - **CYP2C6 and CYP3A2 demonstrated no change or decreased metabolic activity**
- **The majority of the results of these animal studies of CYP450-mediated metabolism disagree with the findings from human studies of AKI**

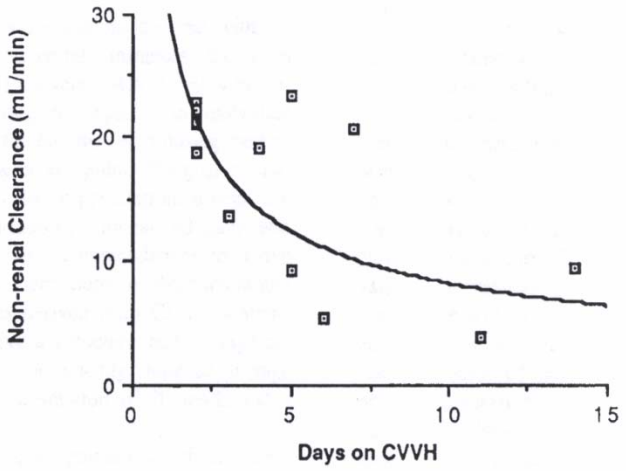
Rat CYP450	AKI model	Effect of AKI on CYP450 metabolic activity
2A1	Uranyl nitrate	⟷
2B1/2	Uranyl nitrate	⟷
2C6	Nephrectomy	⟷
	Bilateral ureter ligation	⟷
	Glycerol	⟷
	Cisplatin	↓
2C11	Uranyl nitrate	↓
2D2	Nephrectomy	⟷
	Bilateral ureter ligation	⟷
	Glycerol	⟷
	Cisplatin	⟷
2E1	Uranyl nitrate	↑
3A1 (3A23)	Uranyl nitrate	↑
3A2	Nephrectomy	↓
	Bilateral ureter ligation	⟷
	Glycerol	↓
	Cisplatin	⟷

Adapted from Vilay AM et al. Critical Care,2008.

AKI and CYP450-mediated metabolism

Human studies

- Macias et al. evaluated the evaluated pharmacokinetics of vancomycin in AKI patients receiving continuous hemofiltration
- Nonrenal clearance was initially preserved early in the course of AKI, but eventually approached the clearance of CKD patients
- Mueller et al. and Vos et al. obtained similar results in studies of continuous hemofiltration and imipenem
- Unknown what precisely constitutes nonrenal clearance in these studies
  - Is this nonrenal clearance hepatic?
- Interestingly, nonrenal clearance was decreased despite concomitant uremic solute removal



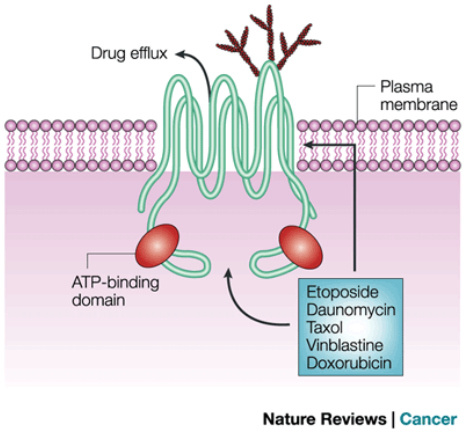
Macias WL, et al. Clin Pharmacol Ther, 1991.

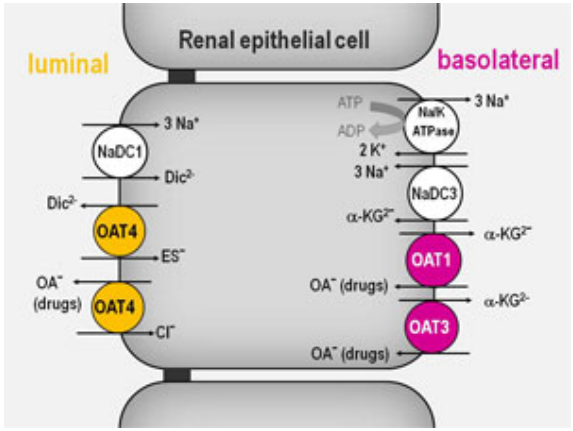
AKI and CYP450-mediated metabolism

- Heinemeyer et al. evaluated pharmacokinetics of metamizole and its primary metabolite monomethylaminoantipyrine (MMAAP) in critically-ill patients with AKI
  - Found reduced clearance of MMAAP in AKI patients
    - Researchers suggested this was secondary to decreased hepatic metabolism
  - However, there are several potential confounders
    - Clinical complexity of the critically-ill patient
      - Hypoxia, decreased protein synthesis, decreased hepatic perfusion, metabolic inhibition from other medications
      - Precise metabolic disposition of metamizole is currently unknown
        - » Metamizole is an inducer of CYP2B6 and 3A4
        - » 4-methylaminopyrine metabolite undergoes enzymatic metabolism with human liver microsomes
        - » No specific CYP450 isoenzyme has been identified for metamizole

AKI and drug transport

- Drug transporters are found in liver, kidney, intestines, brain and pancreas
  - Two major classes
    - Efflux
      - » Excrete drugs from within cells to extracellular space
      - » P-gp (p-glycoprotein)
    - Uptake
      - » Facilitate translocation of drugs into cells
      - » OAT (organic anion transporter)
- Few studies of transporters in AKI





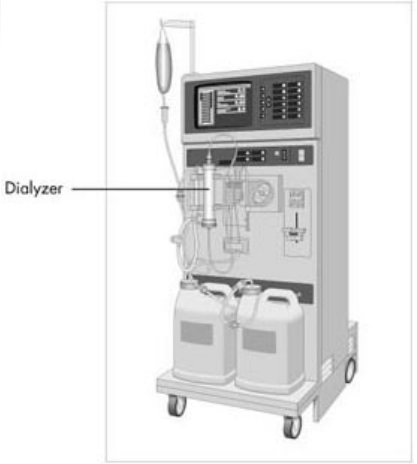
Figures: biotechnica.com andSorrentino et al. Nature Reviews, Cancer 2002.

AKI and drug transport

- Studies of animal models of CKD have shown decreased expression and activity of drug transporters
- Studies of rat models of AKI have been similar
  - Increased P-gp expression in the kidney, but not in liver or intestines
    - Despite increased P-gp expression, renal clearance of P-gp substrate was reduced
    - Decreased clearance also observed in liver and intestines
    - Researchers concluded that AKI causes a systemic suppression of P-gp function
  - In studies of OAT transporters (rOAT1 and rOAT3)
    - rOAT1 and rOAT3 mRNA and expression were reduced
    - Resulted in decreased renal uptake and clearance of the rOAT substrate, p-aminohippurate

Renal replacement therapy and non-renal clearance

- Research by Nolin et al. demonstrated that 4 hours of hemodialysis increased the non-renal clearance of erythromycin in human subjects by 27%
  - Results suggested that inhibitory uremic solutes affect CYP3A4 and transporters in combination or independently
- Subsequent hemodialysis study by Nolin et al. implicated transporters (hOATP and/or intestinal P-gp) as the likely drug disposition bottle-neck in uremia rather than CYP3A4
- Similar improvement in nonrenal clearance would be expected of AKI patients receiving hemodialysis
  - Studies of vancomycin and imipenem and hemofiltration suggest that this may be more apparent later in AKI course when nonrenal clearance has attenuated
  - May be a limit to magnitude of improvement in nonrenal clearance that can be expected from hemodialysis

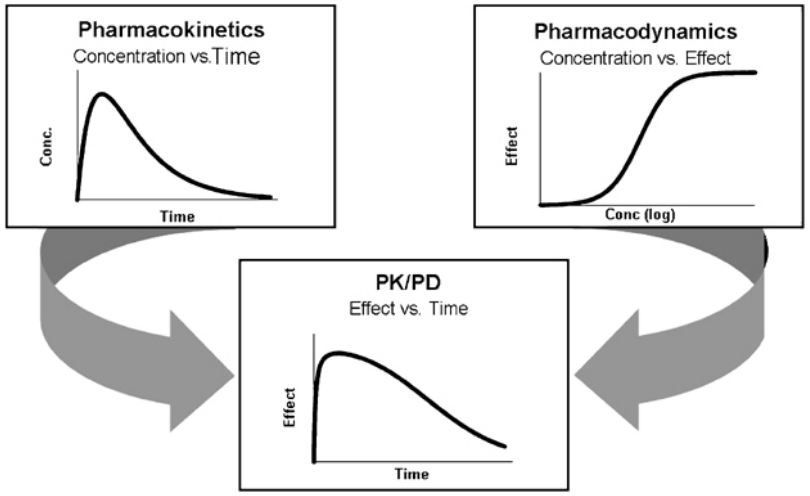


Drug dosing recommendations

- **Majority of animal data demonstrated no effect on CYP450-mediated metabolism from AKI, however drug transport was attenuated**
- **Human AKI studies appear congruent with CKD literature and support a negative effect on nonrenal clearance**
- Given uncertainty of current AKI and non-renal clearance literature, clinically meaningful conclusions are premature
  - Various animal models of AKI may be affecting non-renal clearance differently
  - Extrapolating findings with animal CYP450 enzymes to humans should be done with caution
  - Cannot reliably extrapolate the effect of AKI on the metabolic activity of one metabolic organ such as the liver to another
  - Human studies of the critically-ill introduce uncertainty
    - Precise nature of nonrenal clearance of vancomycin and imipenem is unknown
    - Metamizole metabolic pathway is incompletely characterized
    - Clinical complexity and medical regimens of the critically-ill subjects may introduce confounding variables and influence drug disposition

Drug dosing recommendations

- Recommendations for metabolized medications in AKI include more close monitoring than current clinical practice
  - Frequent monitoring of drug pharmacodynamics
  - Therapeutic drug monitoring/pharmacokinetic analysis
    - Limited by availability of laboratory testing in clinically relevant time-frame
- Duration of AKI may also be important
  - Using dosing recommendations for CKD and ESRD early in AKI for drugs with a significant nonrenal clearance component may lead to subtherapeutic levels
  - Higher dosing may be needed early in course with later reduction in dose and/or frequency as AKI persists and nonrenal clearance attenuates



Mehotra N, et al. Int J Imp Res, 2007.

Future research directions

- More accurate assessments of renal and hepatic function in the setting of AKI
- Human studies of AKI and nonrenal clearance
  - CYP450-mediated metabolism
  - Drug transport
- Elucidation of nonrenal clearance component of medications
- Studies of AKI, renal replacement therapies and nonrenal clearance are needed
- Development of rapid, clinically-relevant laboratory testing of the critical metabolized medications

Breakout Group 4: Discussion Questions/Objectives

- How does total body fluid overload change a drugs volume of distribution?
  - What drugs are more or less affected by changes in volume of distribution?
- How can drug therapies be managed in a proactive versus retroactive manner?
- What clearance equations are pertinent in patients with AKI?

Breakout Group 4: Discussion Questions/Objectives

- **What are the methodological issues and limitations for research of AKI and nonrenal clearance?**
  - **Animal studies**
  - **Human studies**
    - **Renal replacement therapies**
- **What are the most important research studies to start now?**
  - **Focus on most critical metabolic pathways/medications?**
- **What clinically meaningful dosing recommendations can be made for metabolized medications in AKI?**

Breakout Group 4: Clinical Recommendations

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Breakout Group 4: Research & Regulatory Recommendations

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