Dosage Adjustment in Renal Replacement Therapy

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Drug Dosing in AKI and CKD

- Acute Kidney Injury (AKI)
- Chronic Kidney Disease (CKD)

Kidney Disease: Improving Global Outcomes (KDIGO)
- Controversies Conference titled ‘Drug Prescribing in Kidney Disease: Initiative for Improved Dosing’.
- US Food and Drug Administration (FDA)
- European Medicines Agency (EMA)
- for the optimization of pharmacotherapy in the most common clinical practice settings.
There was no regulatory agency guidance during the 1970s to early 1990s that provided a framework for when investigations should be conducted and with what degree of rigor.

Comprehensive evaluations of clinical PK and PD of drugs and the resultant drug dosage regimen adjustment recommendations for CKD patients has been the topic of hundreds of articles in the past two decades and has become a standard feature in almost all clinical pharmacology and therapeutics textbooks.
The Critical Questions

• What patient assessment considerations should be factored into the decision-making process?
• What is the most accurate and reliable index of ‘kidney function’ for drug dosing?
• What are the determinates of the desired therapeutic end points that guide therapy, the significance of risk associated with the accumulation of excessive drug and/or metabolite concentrations, and the degree of impact of AKI or CKD on the PK or PD of a drug?
• How to make pharmaceutical company derived drug PK and PD readily available to clinicians?
• What is the predictive performance of the various methodologies to calculate the desired dosage regimen?
• What are the essential criteria that need to be met to reliably quantify the influence of RRTs on a drug PK and PD, which mathematical methods should be used to individualize drug therapy for those receiving RRTs?
• What educational efforts should be developed to enhance drug prescribing for patients with AKI and CKD?
ASSESSMENT OF KIDNEY FUNCTION

Cockcroft & Gault’s Equation

\[
\text{Clcr} = \frac{(140-\text{age})(\text{LBW})}{72} \times 0.85 \text{ if female}
\]

Unit = mL/min

Unit = mL/min/1.73 m\(^2\), A 70 kg/1.73 m\(^2\) BSA is assumed

ASSESSMENT OF KIDNEY FUNCTION

Modification of Diet in Renal Disease (MDRD) Study Equation

\[
GFR = 186 \times (\text{Scr})^{-1.154} \times (\text{Age})^{-0.203} \\
\times (0.742 \text{ if female}) \\
\times (1.210 \text{ if african-american}) \\
\times (1.129 \text{ in Thai population})***
\]

*Age >18 year-old

**Unit = mL/min/1.73 m^2, > 60 mL/min/1.73 m^2 is not exact number


ASSESSMENT OF KIDNEY FUNCTION

Modification of Diet in Renal Disease (MDRD) Study Equation for IDMS* serum creatinine

GFR = 175.6 × Scr⁻¹.¹⁵⁴ × Age⁻⁰.²⁰³
× 1.212 [black]
× 0.742 [female]

*Isotope Dilution Mass Spectroscopy
**Unit = mL/min/1.73 m², > 60 mL/min/1.73m² is not exact number

# Estimated Baseline Creatinine Based on MDRD Formula

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<th>AGE</th>
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<td>1.1</td>
<td>0.8</td>
</tr>
<tr>
<td>&gt;65</td>
<td>1.0</td>
<td>0.8</td>
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Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI)

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

- \(\kappa\) 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
- max indicates the maximum of Scr/\(\kappa\) or 1
- age is measured in years

*It is more accurate than the MDRD Study equation, particularly at higher levels of GFR*

Children < 12 year-old

Schwartz’s Equation

\[ \text{CrCl} = \left[ K \times \text{Height in cm} \right] / \text{SCr} \]

Where

- \( K = 0.45 \) for infants (younger than 1 year),
- \( K = 0.55 \) for children and adolescent girls, and
- \( K = 0.7 \) for adolescent boys

Unit = (mL/minute/1.73 m\(^2\))

Counahan-Barratt’s Equation

\[ \text{GFR} = \left[ 0.45 \times \text{Height in cm} \right] / \text{SCr} \]

Unit = (mL/minute/1.73 m\(^2\))
• The National Kidney Disease Education Program (NDKEP) in the United States recommends that the GFR estimated from the MDRD Study or CLcr estimates from the CG equation for adults or the Schwartz equation for children can be used for drug dosing.

• For very large or very small people, they recommend adjustment of the estimated GFR (eGFR) from the MDRD Study equation to account for patient’s body surface area (BSA)

\[
(eGFR_{IND} = eGFR_{MDRD} \times (BSA \text{ per } 1.73m^2))
\]

• Clinical laboratories should report eGFR in ml/min as well as ml/min/1.73m\(^2\)
PK and PD data

- Vd increased in patients with moderate to severe CKD, preexisting CKD who develop AKI.
- alterations in nonrenal clearance
  - uptake and efflux transporters
  - CYP enzymes in the liver and other organs
- exposed to a new pharmacologic entity as the sum of
  - the serum concentrations of the metabolite(s)
  - the parent compound
Goals Therapy

• The maintenance of a similar peak, trough, or average steady-state drug concentration

• for antibiotics an optimized PD measure e.g., the time above MIC, the ratio AUC to MIC

• specific target values (Therapeutic range)
Drug Dosage Regimen Individualization

**Loading Dose**
- Loading doses may be required if a drug has a long half-life and there is a need to rapidly achieve the desired steady-state concentrations.

\[
\text{Patient’s loading dose} = \text{Usual loading dose} \times \left[\frac{\text{Patient’s VD}}{\text{Normal VD}}\right]
\]

**Maintenance Dose**
- In general, prolonging the dosing interval but maintaining the same dose will result in the achievement of similar peak and trough concs and AUC

**Measurement of Therapeutic Drug Levels**
DRUG DOSAGE CONSIDERATIONS FOR PATIENTS WITH Acute Kidney Injury (AKI)

PK and PD data

- Critically ill patients
  - AKI
  - Multiorgan dysfunction syndrome (MODS) or Multisystem organ failure (MSOF).

- Limit knowledge of drug metabolism and disposition in pt. with MSOF/MODS and AKI

- Absorption-altering conditions
  - eg., slow gastrointestinal motility, prolonged intestinal transit times, bacterial colonization, and necrotizing enterocolitis

- Hypoxia
  - decreased protein synthesis, competitive, inhibition from concomitant medications, and decreased hepatic perfusion
DRUG DOSAGE CONSIDERATIONS FOR PATIENTS WITH “AKI”

Patient Assessment

• Hyperfiltration and massive overhydration are often evident early in the course of MSOF/MODS, esp. burns or trauma
• Inappropriately low doses of medication
• Creatinine needs to be measured at steady state
• “No estimating equations can provide an accurate estimate of GFR in AKI”
Loading Dose

- **Increased Vd** of hydrophilic antibiotics, including β-lactams, cephalosporins, and carbapenems.
- Aggressive loading doses (25–50% greater than normal) are highly recommended.

Maintenance Dose

- Preservation of nonrenal clearance for some agents eg., vancomycin, imipenem, and ceftizoxime.
- The tendency to attain a positive fluid balance in the early stages of AKI.
- The dosing regimen esp. antimicrobial agents, should be initiated at normal or near-normal dosage regimens.

Therapeutic Drug Monitoring
DRUG DOSAGE CONSIDERATIONS FOR PATIENTS WITH “AKI”

• The KDIGO AKI, AKIN, RIFLE, or pRIFLE criteria should be prospectively utilized to optimize the identification of patients at highest risk of developing AKI.

• High-risk medications, those with known nephrotoxicity, or other potential toxicities associated with supratherapeutic serum concs should be identified proactively.

• Vd of several medications is dramatically increased in the presence of AKI and thus larger loading doses may need to be administered to avoid subtherapeutic responses due to the achievement of lower than desired serum concentrations.

• When possible, TDM should be utilized for those medications where serum drug concs can be obtained in a clinically relevant time frame.

• Trends in renal function indices (Scr and urine output) along with volume status should be utilized to guide drug dosing when rapidly measurable indices are unavailable.

• For those medications where TDM is not possible, close monitoring of drug PD may prove to be a useful surrogate.
Concentration gradient based transfer. Small molecular weight substances (<500 Daltons) are transferred more rapidly.
Movement of water across the membrane carries solute across the membrane.

Middle molecules are removed more efficiently.
PK and PD data

• **Drug-related factors**
  – MW or size, degree of protein binding, and distribution volume.

• **Dialysis filters in use until the mid 1990s**
  – cellulose, cellulose acetate, or regenerated cellulose (cuprophane)
  – impermeable to drugs with $MW > 1000$ Daltons

• **Dialysis membranes in the 21st century**
  – semi-synthetic or synthetic materials (eg., polysulfone, polymethylmethacrylate, or polyacrylonitrile).

• **High-flux dialysis membranes**
  – larger pore sizes
  – allows the passage of most solutes including drugs that have a $MW \leq 20,000$ Daltons
Assessment of the impact of HD dialyzer clearance (CL$_D$) of the drug;

\[
\text{CL}_D^b = Q_b \left[ \frac{(A_b - V_b)}{A_b} \right]
\]

where

- $Q_b$ = blood flow through the dialyzer
- $A_b$ = concentration of drug in blood going into the dialyzer
- $V_b$ = blood concentration of drug leaving the dialyzer.
Assessment of the impact of HD dialyzer clearance ($CL_D$) of the drug;

$$CL_D^p = Q_p \left[ \frac{(A_p - V_p)}{A_p} \right]$$

where

- $Q_b =$ plasma flow $= Q_b(1$-Hematocrit$)$
- $A_p =$ concentration of drug in plasma going into the dialyzer
- $V_p =$ plasma concentration of drug leaving the dialyzer.

- tends to underestimate HD clearance for drugs that readily partition into and out of erythrocytes.
- venous plasma concs may be artificially high if extensive ultrafiltration is performed.
Assessment of the impact of HD

Recovery clearance ($CL_{D}^r$) of the drug;

$$CL_{D}^r = R/AUC_{0→t}$$

where

- $R =$ Total amount of drug recovered unchanged in the dialysate
- $AUC_{0→t} =$ area under the predialyzer plasma concentration–time curve during the period of time that the dialysate was collected
Assessment of the impact of HD

- **TDM** and measurement of the dialyzer clearance should be utilized for drugs with a narrow therapeutic range (AMGs, Vancomycin)

- Drug dosage recommendations derived from studies conducted before 2000
  - Likely represent an underestimate of the impact of HD
  - Dosages may need to be empirically increased by 25–50%
DRUG DOSING CONSIDERATIONS FOR HD PATIENTS

\[ D_{hd} = D_{fail} + D_{sup} \]

where

- \( D_{hd} \) = Dose after dialysis
- \( D_{sup} \) = Supplementary dose; \( D_{sup} = Fr \times (D_{start} - D_{fail}) \)
  - \( Fr \) = the fraction removed by dialysis
  - \( D_{fail} \) = dose adjusted to kidney failure

- The \( D_{sup} \) derived from studies of low-flux nonsynthetic membranes should empirically be increased by at least 50% when pt are dialyzed with high-flux synthetic dialyzers
- Extended dialysis regimens with high diffusive membranes have been associated with extensive drug clearances and thus the \( D_{sup} \) may need to be increased
Redistribution of vancomycin after low flux hemodialysis
DRUG DOSING CONSIDERATIONS FOR PATIENTS RECEIVING Continuous Renal Replacement Therapy (CRRT)

CRRT

• commonly used to manage hemodynamically unstable AKI patients
• Several modes of therapy
  – convective, diffusive, or both
• variety of filter materials
• different effluent flow rates
• continuous venovenous hemofiltration (CVVH)
DRUG DOSING CONSIDERATIONS FOR PATIENTS RECEIVING CRRT

Hybrid RRTs

- utilize higher dialysate flow rates
- shorter treatment periods (6–12 h in duration)
- Limited PK data

Hybrid therapies

- slow low-efficiency dialysis (SLED)
- Extended daily dialysis (EDD)
- continuous SLED
- slow low-efficiency daily dialysis (SLEDD)
- slow low-efficiency daily hemodiafiltration (SLEDD-f)
Assessment of the impact of CRRT and hybrid RRT

- The mode of therapy (diffusion, convection, or both) can be influential, as both therapy modes can remove small solutes, but convective therapies are superior at removing larger solutes
Drug dosing approaches (1)

- **ESRD dosing recommendations** should be used only as an initial guide for the initiation of therapy in an AKI patient receiving CRRT when no other information is available.

- The existing maintenance dosing recommendations for ESRD patients receiving HD *often result in the achievement of subtherapeutic concentrations* and treatment failures for patients with severe AKI requiring RRT.
Drug dosing approaches (2)

- The most effective dosing optimization strategy is to use TDM for drugs like AMGs and vancomycin. However, very few drugs have clinically useful (quick turnaround time, FDA/EMA approved) assays available.
Drug dosing approaches (3)

- When CRRT or EDD clearance data are available, the current literature recommendations should be the logical starting dose for therapy.
- Different treatment intensities for CRRT or EDD result in marked variability in drug removal and thus this literature may not be generalizable across the multiple CRRT and EDD prescriptions that are used in practice.
Drug dosing approaches (4)/1

• Calculate the “total creatinine clearance (CLcr)” based on the addition of
  – The patient’s residual renal clearance
  – Expected extracorporeal clearance.

• This value can then be used to estimate a maintenance dosing regimen based on medication dosing guidelines specified for that resultant total CLcr range.

• Using this method, most drugs will fall in the CLcr 25–50 ml/min range
Drug dosing approaches (4)/2

• starts with the dose and dosing interval for a patient with a GFR < 10 ml/min (anuric dose)
• makes dosage adaptations based on the drug fraction expected to be removed by extracorporeal therapy (FrEC)

Maintenance dose = anuric dose/[1 - FrEC]

Dosing interval = anuric dosing interval \times [1-FrEC]
Drug dosing approaches (5)

- starts with a normal dose ($D_n$) and reduces dose based on normal clearance ($Cl_{\text{norm}}$), non-renal clearance ($Cl_{\text{nonrenal}}$), effluent rate ($Q_{\text{eff}}$), and sieving coefficient ($SC$)

\[
Dose = Dose_n \times \frac{Cl_{\text{nonrenal}} + (Q_{\text{eff}} \times SC)}{Cl_{\text{norm}}}
\]
Purpose of review
Continuous renal replacement therapy is increasingly used in the management of acute kidney injury in critically ill patients. The potential extracorporeal removal of drugs, in particular the removal of antimicrobials, is a concern to many clinicians. The results of clinical studies cannot be generalized because different treatment modalities and settings are used in heterogeneous patient populations. This review aims to provide general guidelines for drug dosing during continuous renal replacement therapy.

Recent findings
The basic principles underlying drug removal with different modalities of continuous renal replacement therapy are reviewed and general approaches for drug dosage adaptation are proposed. Dosing should consider extracorporeal clearance, mainly depending on the dose and mode of therapy, type of membrane and protein binding, but also fractional extracorporeal clearance, accounting for hepatic, metabolic and residual renal clearance. Of note, pharmacokinetic variables may be highly variable in the critically ill. Appropriate dosing of antimicrobials additionally requires the application of pharmacodynamic principles. For nontoxic antimicrobials, the clinician should prefer slight overdosing while monitoring of plasma concentrations is crucial for drugs with a narrow therapeutic index.

Summary
Drug dosage adaptation during continuous renal replacement therapy can use several approaches, which all include a degree of unpredictability and thus require maximal reliance on drug monitoring.

Keywords
acute kidney injury, continuous renal replacement therapy, drug elimination, pharmacodynamics

Abbreviations
AKI acute kidney injury
AUC area under the plasma concentration versus time curve
CRRT continuous renal replacement therapy
MIC minimal inhibitory concentration
RRT renal replacement therapy

Introduction
Acute kidney injury (AKI) requiring renal replacement therapy (RRT) occurs in 5% of ICU patients [1]. Continuous RRT (CRRT) is increasingly used in the management of these patients, especially in Europe, Asia and Australia [2]. ICU patients requiring RRT represent a very heterogeneous population with mostly high illness severity and failure of several other organs (multiple organ dysfunction). They frequently need multiple drugs, many of which have vital indications and therefore require adequate dosing. In view of the existing organ dysfunction, however, the tolerance towards the toxic effects of drug overdosing is decreased.

Correct drug dosing in ICU patients with CRRT is extremely difficult because extracorporeal drug removal is superimposed on the disturbed pharmacokinetics induced by critical illness. In addition, the clinical situation may change rapidly over time. The available literature on the removal of individual drugs with CRRT is limited and the results are not generalizable in view of the wide variation in CRRT techniques and settings and the heterogeneity of the patient population. Drug dosing in CRRT patients should therefore use an individualized approach. Rather than providing dosing guidelines for individual drugs, this review aims to describe the general principles that should enable clinicians to reduce the risk of improper drug dosing during CRRT.

Pharmacokinetics and pharmacodynamics in the critically ill
Correct drug dosing during CRRT requires an understanding of basic pharmacokinetic parameters including protein binding, volume of distribution and clearance that determine the peak and trough concentration ($C_{\text{max}}$ and $C_{\text{min}}$), the half-life and the area under the plasma concentration versus time curve (AUC). Critical illness may have marked effects on pharmacokinetics (reviewed in [3,4,5,6,7]) and data from healthy volunteers cannot

DRUG DOSING CONSIDERATIONS FOR PATIENTS RECEIVING PERITONEAL DIALYSIS

• Most typical peritoneal dialysis prescriptions are designed to achieve a urea clearance of ~10 ml/min.
• Enhance total body clearance of any drugs by more than 10 ml/min.
• Most drugs are larger than urea, their clearance is even less; thus, drug clearance will likely be in the range of 5 to 7.5 ml/min.
• Drug therapy recommendations for those with CLcr or eGFR < 15 ml/min are likely clinically useful.
Figure 30-7 Continuous ambulatory peritoneal dialysis. (A) The peritoneal catheter is implanted through the abdominal wall. (B) Dacron cuffs and a subcutaneous tunnel provide protection against bacterial infection. (C) Dialysate flows by gravity into the peritoneal catheter and then into the peritoneal cavity until the next drainage period. Dialysis thus continues on a 24-hour-a-day basis during which the patient is free to move around and engage in his or her usual activities. (Used with permission from Smeltzer SC, Bare BG: Brunner & Suddarth's Textbook of Medical-Surgical Nursing [10th Ed], p 1293. Philadelphia, Lippincott Williams & Wilkins, 2004.)

Continuous ambulatory peritoneal dialysis (CAPD), Nocturnal intermittent peritoneal dialysis (NIPD), Continuous cycling peritoneal dialysis (CCPD), Nocturnal tidal peritoneal dialysis (NTPD)
Intraperitoneal Drug Administration

- Mostly use in PD associated peritonitis (infections)
- Solubility and stability of the compounds in peritoneal dialysis fluid
- Co-administration of more than one compound can lead to chemical interactions and changes in solubility.
- Administration intervals depend on the half-life of the drug, which is mainly determined by residual renal and extrarenal metabolic clearance.
DRUG DOSING CONSIDERATIONS FOR PATIENTS RECEIVING “PERITONEAL DIALYSIS”

• peritoneal antibiotic doses have used 4- to 8-h loading periods, it is recommended to perform antibiotic loading by an extended cycle in both CAPD and Automated peritoneal dialysis (APD) patients.

• Intermittent maintenance dosing,
  – a long night-time dwell should be used in CAPD
  – a long day-time dwell in APD patients
DRUG DOSING CONSIDERATIONS FOR PATIENTS RECEIVING “PERITONEAL DIALYSIS”

• Transperitoneal drug movement may be less effective in the post acute phase of peritoneal infection when inflammation-related capillary hyperperfusion subsides.

• Monitoring of drug blood levels is advocated in patients receiving intraperitoneal antibiotics because they are at increased risk or under- and over-dosing, that is, those with significant residual renal function and those on intense APD schedules, respectively.

• Monitoring of dialysate concentrations may provide even more relevant information.
Resources
