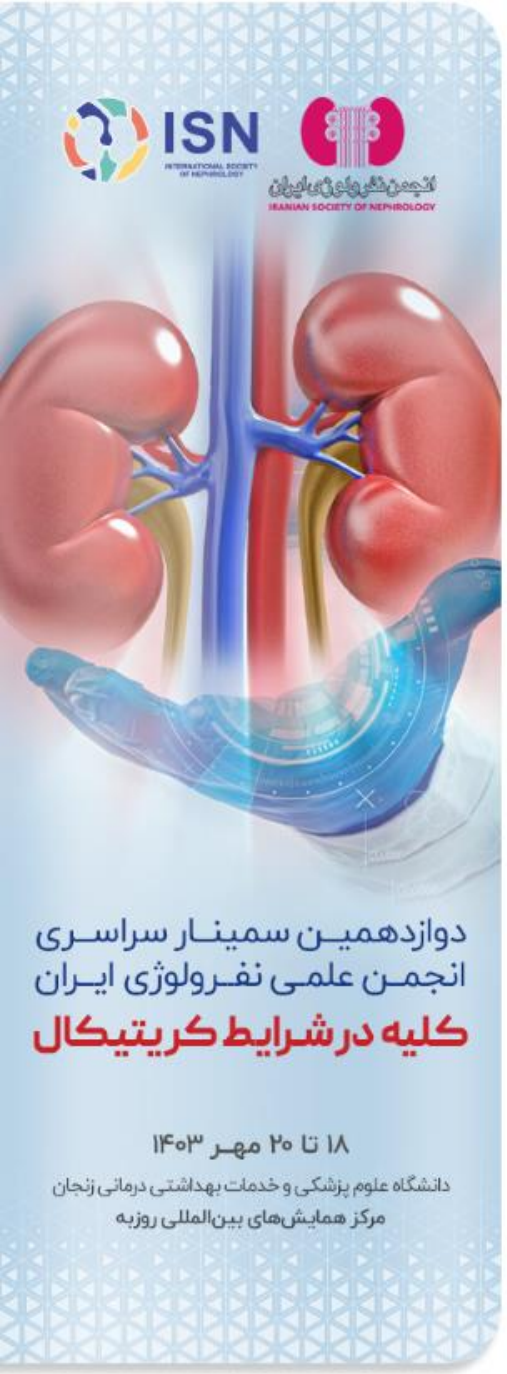

Optimizing Pharmacotherapy in AKI: Pharmacokinetic Considerations

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Introduction

- Appropriate drug dosing in AKI patients is a challenge to the intensivists due to various factors such as:

a) **Patient related** (appropriate body weight, organ clearance, serum protein concentration),

b) **Drug related** [MW, PB, Vd, hydrophilicity, or hydrophobicity], and

c) **RRT related** (type, modality of solute removal, filter characteristics, dose and duration)

Core principles

- The pharmacokinetics and pharmacodynamics of many drugs are altered in patients with impaired kidney function.
- Dosages of drugs that are cleared by the kidneys should be adjusted according to the patient's kidney function.
- Many drugs have a narrow therapeutic window, for which there may be lack of efficacy with subtherapeutic levels and adverse events associated with elevated levels.
- TDM should be performed to achieve the desired target concentration.

Core principles

- Kidney replacement therapy can have a significant influence on the extracorporeal removal of drug.

- Biotransformation of drugs may be altered in patients with kidney failure. Active or toxic metabolites may accumulate in patients with kidney failure, leading to adverse effects.

- Excipients such as diluents can also accumulate in the setting of kidney failure, resulting in toxicity.

Alterations in Pharmacokinetic Parameters

❑ Absorption, Distribution, Metabolism, and Elimination

❖ Change in BA in uremia by:

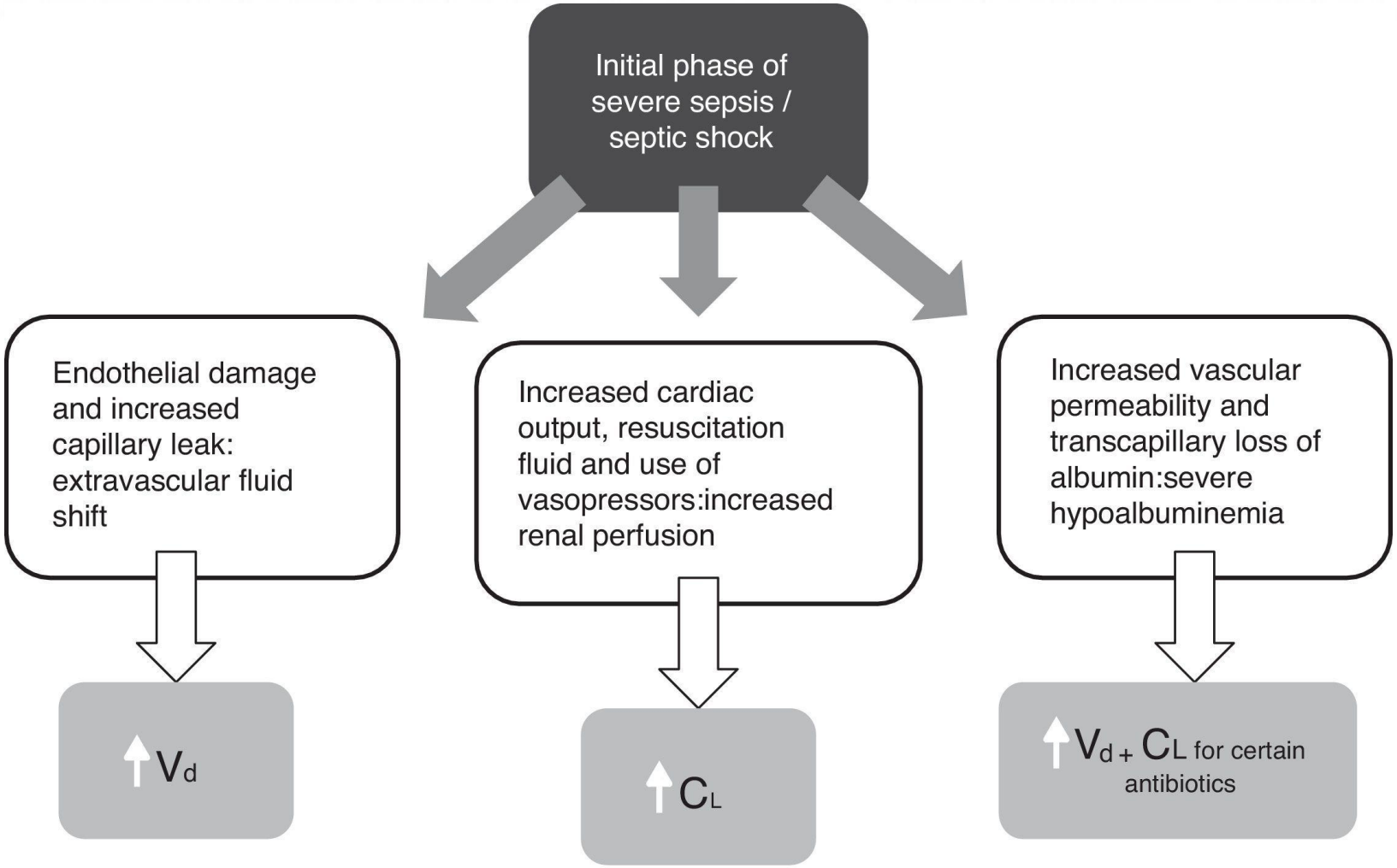
- Nausea, vomiting, diarrhea, gastritis, or edema of the GI tract
- ↓ Gastric and intestinal motility, as well as gastric emptying time
- ↑ Gastric ammonia, ↑ gastric pH
- ↓ Intestinal P-glycoprotein activity
- Vasoactive agents ➲ ↓ blood flow to the GI tract and SC tissues and ↓ gastric motility
- Antibiotics may adhere to the feeding tubes or interact with coadministered nutritional products and other drugs

Distribution

- Kidney failure➲ alterations in plasma protein binding ➲ ↑unbound drug
- Low serum albumin levels in AKI due to increased vascular permeability, protein catabolism, malnutrition, and/or acute illness.

- Fluid overload could dilute the serum concentrations of antibiotics resulting in decreased efficacy and contribute to the increased mortality rate.

- The Vd in critically ill patients can increase by more than 100% (antibiotic *Vd* varies ten-fold or more)



V_d – volume of distribution C_L – clearance

Metabolism

- Depending on the etiology of AKI, nonrenal clearance appears to be preserved early in the course of illness.
- Patients with AKI brought on by septic shock in the acute phase may be aggressively fluid resuscitated ➲ ↑ hepatic blood flow and hepatic metabolism.
- Vasopressors ➲ ↓ metabolism due to decreased hepatic blood flow
- Drug-metabolizing capacity of the kidneys (nearly 15% of the metabolic function of the liver)

Elimination

- AKI ➲ 🡅 glomerular permeability, 🡅clearance rates of highly protein-bound drugs.

- For example, in patients with nephrotic syndrome, the glomerular basement membrane loses negative charge and allows albumin and other large molecules to leak across the barrier.

- In patients with AKI, tubular secretion may be decreased as endogenous and exogenous acids and bases accumulate and compete for transporters.

Table 2. - AKI, CKD, and from kidney replacement therapy have differing effects on pharmacokinetics

Pharmacokinetic Parameter	AKI	CKD	Kidney Replacement Therapy
Absorption	Poorly quantified, may decrease	Poorly quantified, may increase or decrease	Limited effect
Volume of distribution	No change or increase	No change or increase	No change or decrease
Metabolism	Poorly quantified, clearance by CYP3A4/5 may decrease	Decreased clearance by several CYPs observed	May increase post-KRT compared with pre-KRT, but the duration and extent of the change is poorly quantified
Excretion	Kidney: decreased, rapidly changing	Kidney: decreased, relatively stable	Kidney: no change
	Nonkidney: unknown	Nonkidney: poorly quantified, possibly decreased	Nonkidney: uncertain
Elimination			Increased because of drug removal by KRT the extent depends on properties of both the drug, the KRT regimen and its duration

CYP, cytochrome-P 450 enzyme.

Dosing Theories in Acute Renal Failure

- Pharmacodynamic (i.e., antimicrobial agents with time-dependent vs. concentration-dependent killing effects) and pharmacokinetic parameters, potential side effects of drug accumulation, and clinical status of patient (i.e., hemodynamic instability, severe inflammatory state, etc.) must be considered to attain this goal.

- Specific medication-related factors (MW, PB, Vd, hydrophilicity, or hydrophobicity) must also be understood.

Loading dose

- The administration of a loading dose before maintenance dosing allows for more rapid achievement of therapeutic plasma concentrations.

$$LD\ (\mathrm{mg}) = \frac{\text{target concentration}\ \left(\mathrm{mg/L}\right) \times Vd\ (\mathrm{L})}{F}.$$

- Because the **Vd** of many drugs, especially **hydrophilic antibiotics**, including β-lactams, cephalosporins, and carbapenems, is significantly increased in the presence of AKI, the administration of proactive **LDs (25-50% > normal)** is highly recommended.

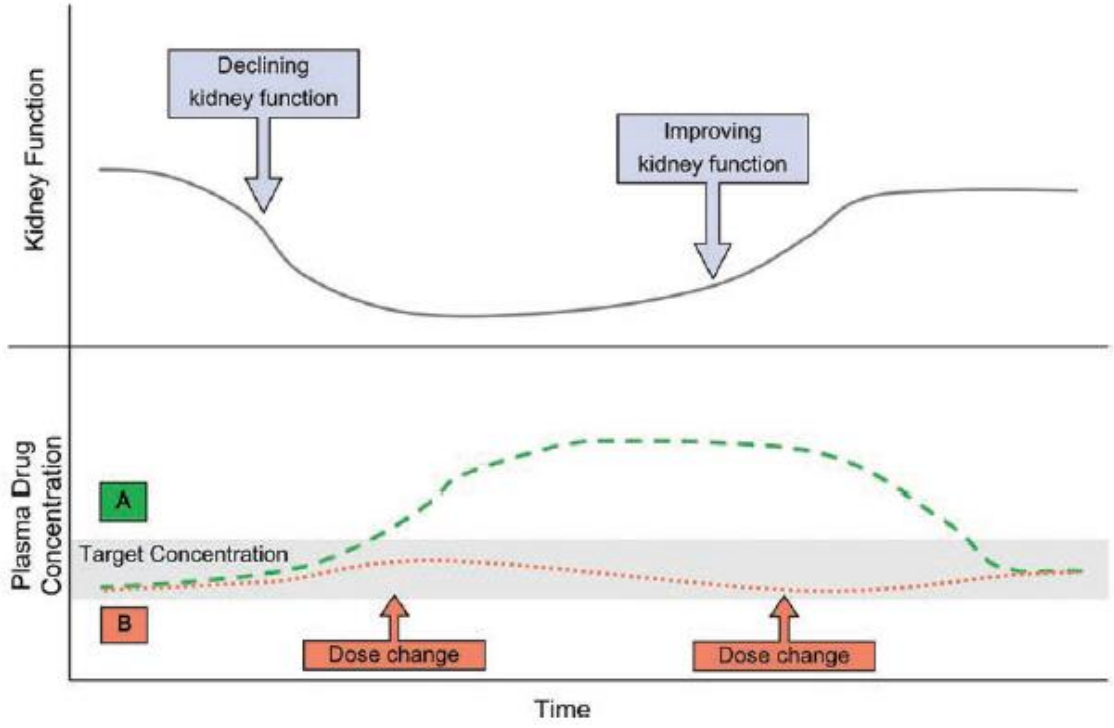
Maintenance Dose

- ↓ dose, ↑ dosing interval, or a combination of both.
- Medications that require higher concentrations to achieve their therapeutic effect should have their interval extended, while those that are likely to accumulate and cause adverse effects may have their dose reduced as well.

$$MD=(Css)\ (Cl)$$

- It is critically important to follow the patient closely and recognize **trends for decreasing or improving kidney function** in an effort to achieve and maintain medication therapy management goals

Relationship between kidney function changes in AKI and dosing of renally eliminated drugs



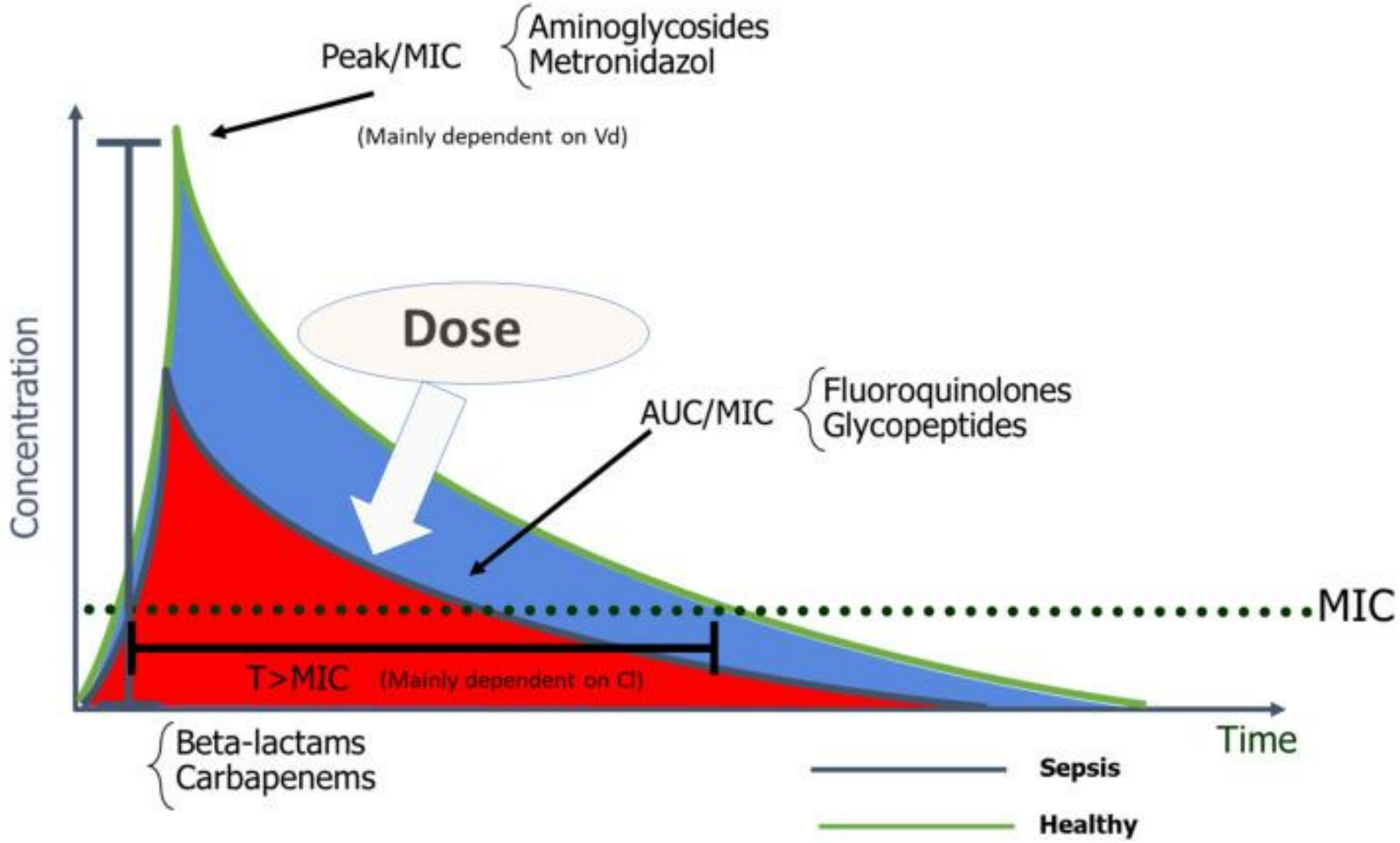

Peak/MIC
Aminoglycosides
Metronidazol
(Mainly dependent on Vd)
Dose
AUC/MIC
Fluoroquinolones
Glycopeptides
Concentration
MIC
T>MIC
(Mainly dependent on Cl)
Time
Beta-lactams
Carbapenems
Sepsis
Healthy

Table 7. Intravenous Antibiotics: Pharmacodynamic Principles to Consider When Adjusting Dose

Drug Class	Drugs	Pharmacodynamic Principle	Pharmacodynamic Parameter to Optimize
Penicillins	Penicillin Piperacillin-tazobactam Ampicillin ± sulbactam Nafcillin[a]	Time dependent	Time > MIC
Cephalosporins	Cefazolin Cefuroxime Cefotetan Cefoxitin Cefotaxime Ceftazidime Ceftriaxone Cefepime Ceftolozane/tazobactam Ceftaroline	Time dependent	Time > MIC
Carbapenems	Imipenem Meropenem Ertapenem Doripenem	Time dependent	Time > MIC
Glycopeptide	Vancomycin	Time dependent	$AUC_{0\text{-}24}$/MIC
Macrolide	Azithromycin[a] Erythromycin Clarithromycin	Time dependent	$AUC_{0\text{-}24}$/MIC
Oxazolidinones	Linezolid[a] Tedizolid[a]	Time dependent	$AUC_{0\text{-}24}$/MIC
Lipopeptides	Daptomycin	Concentration dependent	$AUC_{0\text{-}24}$/MIC
Aminoglycosides	Gentamicin Tobramycin Amikacin	Concentration dependent	C_{max}/MIC; $AUC_{0\text{-}24}$/MIC
Lipoglycopeptides	Telavancin Dalbavancin Oritavancin	Concentration dependent	$AUC_{0\text{-}24}$/MIC
Fluoroquinolones	Levofloxacin Ciprofloxacin Moxifloxacin[a]	Concentration dependent	$AUC_{0\text{-}24}$/MIC; C_{max}/MIC

Abbreviations: $AUC_{0\text{-}24}$, area under the concentration-time curve during a 24-hour period; C_{max}, maximum drug concentration; MIC, minimum inhibitory concentration.
[a]Does not require dosage adjustment for kidney dysfunction

Augmented Renal Clearance Affecting Drug Dosing

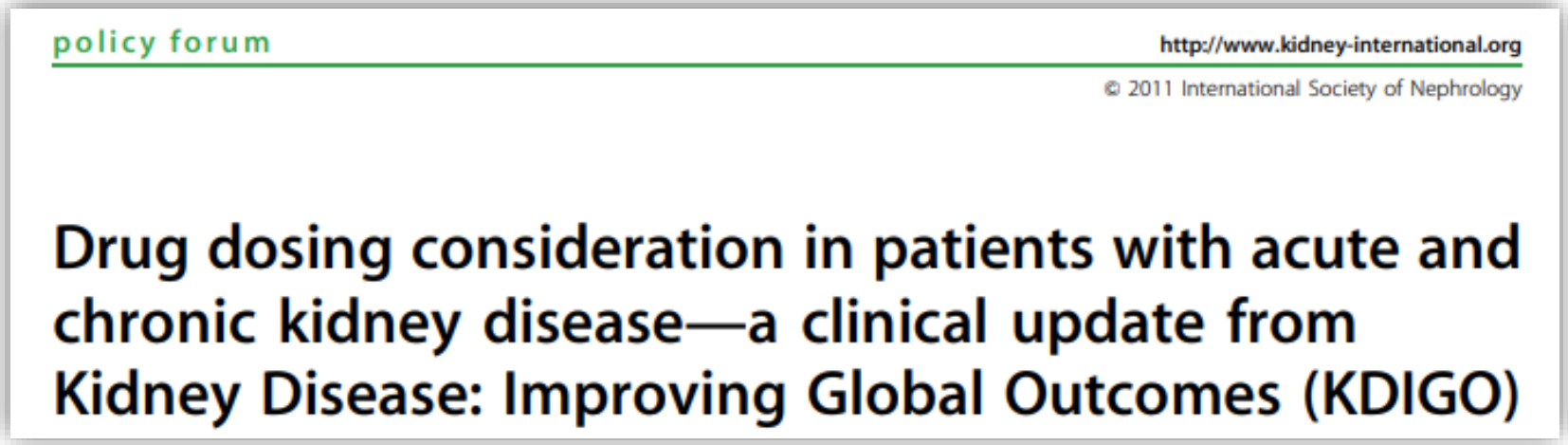
- ARC is defined as estimated GFR >130 mL/minute/1.73 m2 that can happen in the **initial phase** of **sepsis**, **burns**, or **trauma**, where the presence of hyperdynamic circulation ➲ ↑ renal blood flow and glomerular hyperfiltration.

- ARC (20–65% of critically ill patients)➲ underdosing of the drug (especially hydrophilic medications) due to enhanced renal elimination.

Cont.

- Antibiotic dose adjustment in patients with AKI is a complex process and it’s crucial to balance the need for effective treatment against the risk of drug toxicity.

❑ Here are some key points from recent studies:



Because of the preservation of **nonrenal clearance** for some agents such as vancomycin, imipenem, and ceftizoxime, as well as the tendency to attain a **positive fluid balance** in the early stages of AKI, the dosing regimen for many drugs, especially **antimicrobial agents**, should be initiated at normal or nearnormal dosage regimens.

JAC Antimicrob Resist
https://doi.org/10.1093/jacamr/dlac080

JAC-Antimicrobial Resistance

Optimization of antimicrobial dosing in patients with acute kidney injury: a single-centre observational study

Stephen Hughes[1], Katie L. Heard[1], Nabeela Mughal[1,2,3] and Luke S. P. Moore [1,2,3]*

Dose adjustments of β-lactams may **not be necessary** in the first 48 hours of infection-induced AKI.

Open Forum Infectious Diseases

MAJOR ARTICLE

Early Versus Late Antipseudomonal β-Lactam Antibiotic Dose Adjustment in Critically Ill Sepsis Patients With Acute Kidney Injury: A Prospective Observational Cohort Study

early β-lactam (within 24 h) vs late β-lactam (after 24 h)

L-BLA ➲ significant reduction in **in-hospital mortality** compared to E-BLA dose adjustment

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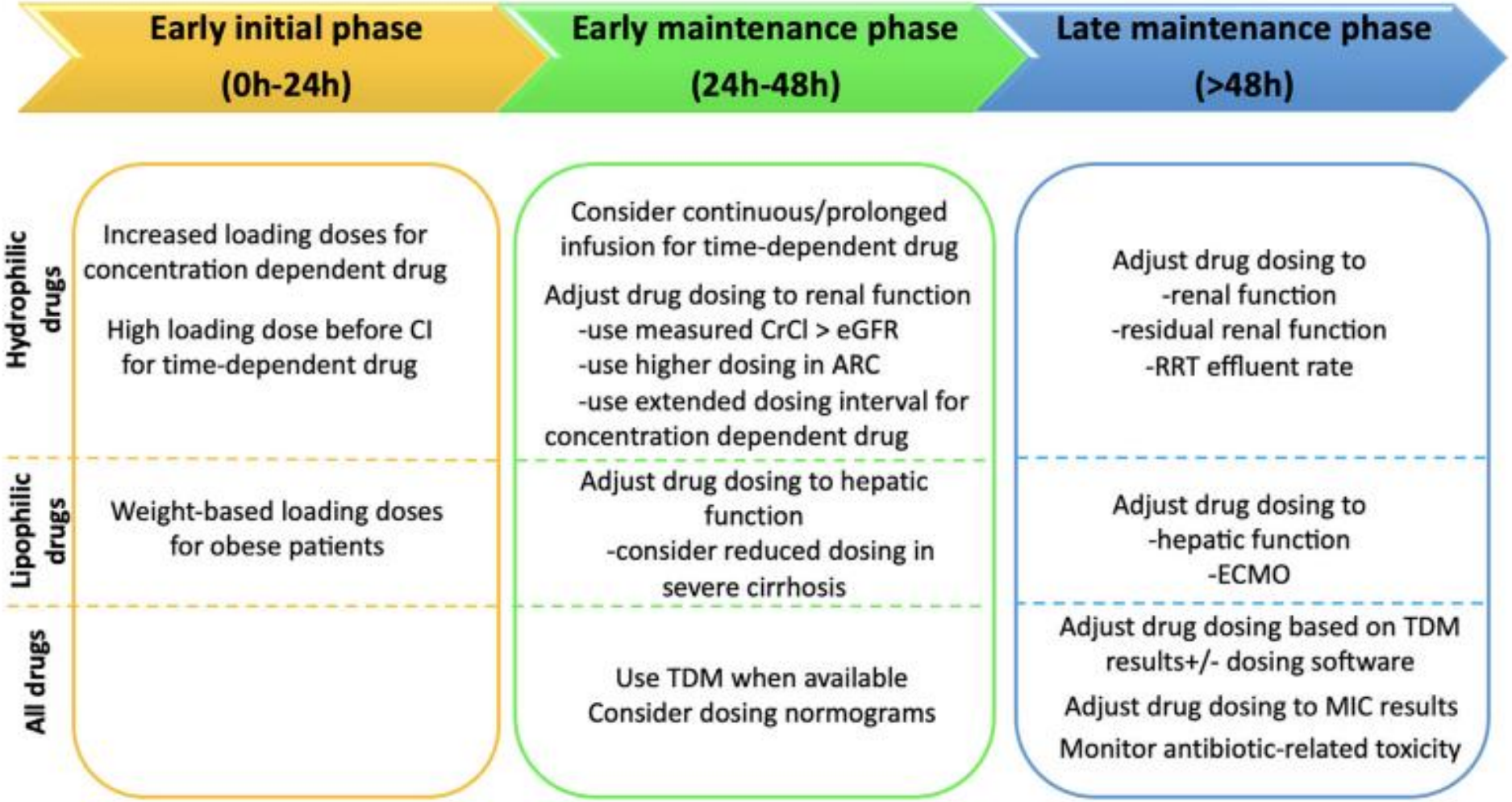
Review

Understanding antimicrobial pharmacokinetics in critically ill patients to optimize antimicrobial therapy: A narrative review


Early initial phase
(0h-24h)
Early maintenance phase
(24h-48h)
Late maintenance phase
(>48h)
Hydrophilic drugs
Increased loading doses for concentration dependent drug
High loading dose before CI for time-dependent drug
Consider continuous/prolonged infusion for time-dependent drug
Adjust drug dosing to renal function
-use measured CrCl > eGFR
-use higher dosing in ARC
-use extended dosing interval for concentration dependent drug
Adjust drug dosing to
-renal function
-residual renal function
-RRT effluent rate
Lipophilic drugs
Weight-based loading doses for obese patients
Adjust drug dosing to hepatic function
-consider reduced dosing in severe cirrhosis
Adjust drug dosing to
-hepatic function
-ECMO
All drugs
Use TDM when available
Consider dosing normograms
Adjust drug dosing based on TDM results+/- dosing software
Adjust drug dosing to MIC results
Monitor antibiotic-related toxicity

- In some situations with sepsis and presence of AKI, immediate reductions in dosing for selected agents such as antibiotics should be cautioned as it may lead to under treatment.

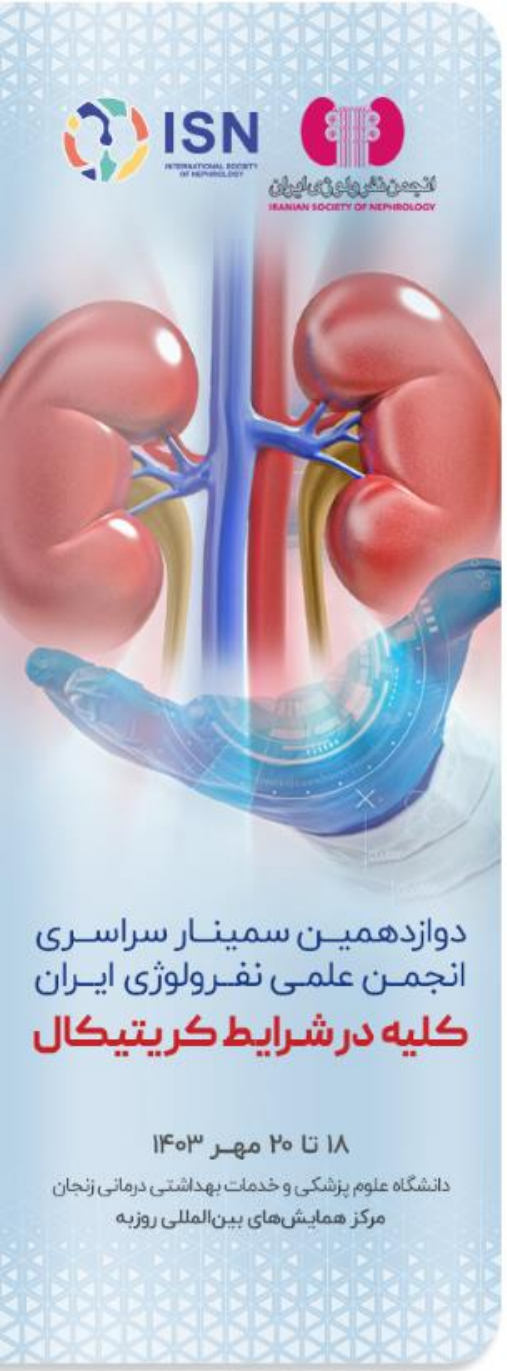
- With the exception of **vancomycin** or **aminoglycosides**, full doses or extended infusions of antibiotics should be considered for the first 24 hours and reevaluated.

Dippiro

- Maintenance dosing regimens for many drugs, especially **antimicrobial** agents, should be **initiated** at **normal or near-normal dosage regimens** and adjustments made based on the relationship between drug PK characteristics and kidney function.

- Prospective measurement of **serum drug concentrations** is recommended.

Brenner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۱۸ تا ۲۰ مهر ۱۴۰۳
دانشگاه علوم پزشکی و خدمات بهداشتی درمانی زنجان
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Thank you