

Dosage adjustment in Renal and hepatic Disease

Renal Impairment

- **Renal impairment** refers to a reduction in kidney function, which impacts the body's ability to excrete waste products and drugs.
- Since the kidneys play a vital role in the elimination of many medications, impaired renal function can lead to **drug accumulation, increased toxicity, and altered therapeutic effects**.

Pathophysiology of Renal Impairment

- Renal impairment can range from mild dysfunction to complete kidney failure.
- Common causes include:
 - Diabetes mellitus
 - Hypertension
 - Glomerulonephritis
 - Polycystic kidney disease
 - Drug-induced nephrotoxicity

Types of Renal Impairment

- Renal impairment can be:
 - **Acute (Acute Kidney Injury, AKI):** Sudden decline in renal function, often reversible.
 - **Chronic (Chronic Kidney Disease, CKD):** Progressive and irreversible deterioration of renal function over time.

Causes of Renal Impairment:

- Acute kidney injury (AKI)
- Chronic kidney disease (CKD)
- Diabetes mellitus
- Hypertension
- Glomerulonephritis
- Drug-induced nephrotoxicity (e.g., NSAIDs, aminoglycosides)

Classification and Staging of Renal Impairment

Renal function is typically assessed using **estimated glomerular filtration rate (eGFR)**. This helps guide diagnosis, monitoring, and drug dose adjustment.

A. General eGFR-based Classification

Severity	eGFR (mL/min/1.73 m ²)	Description
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Normal	>90	Normal kidney function
Mild Impairment	60–89	Slight reduction
Moderate Impairment	30–59	Moderate dysfunction
Severe Impairment	15–29	Severe dysfunction
Kidney Failure (ESRD)	<15	May require dialysis

B. CKD Staging (Based on GFR)

Stage	GFR (mL/min/1.73 m ²)	Description
1	≥90	Normal or high GFR
2	60–89	Mildly decreased
3a	45–59	Mild–moderate decrease
3b	30–44	Moderate–severe
4	15–29	Severe decrease
5	<15	Kidney failure (ESRD)

Impact of Renal Impairment on Drug Therapy

1. Decreased Drug Clearance:

- Drugs primarily excreted via kidneys accumulate in the body.
- Half-life of renally cleared drugs may be significantly prolonged.

2. Altered Pharmacokinetics:

- Changes in absorption, distribution, metabolism, and excretion.
- Fluid overload or proteinuria can alter the **volume of distribution** and **plasma protein binding**.

3. Increased Risk of Adverse Drug Reactions (ADRs):

- Narrow therapeutic index drugs (e.g., digoxin, lithium) are especially risky.

4. Changes in Drug Metabolites:

- Some metabolites, normally cleared by kidneys, can accumulate and be toxic (e.g., normeperidine from meperidine).

5. Impaired Renal Tubular Function:

- May affect the active secretion or reabsorption of certain drugs.

6. Uremia:

- Uremic toxins can alter drug binding to plasma proteins and may interfere with drug metabolism.

Pharmacokinetic Considerations in Renal and Hepatic Disease

- Pharmacokinetics involves how the body **absorbs, distributes, metabolizes, and eliminates** a drug.
- In renal and hepatic disease, these processes can be significantly altered, requiring adjustments in drug dosing to avoid toxicity or therapeutic failure.

Absorption:

A. Renal Disease:

- Usually not significantly affected.
- However, **absorption may be altered by:**
 - Delayed gastric emptying (common in uremia)
 - Altered gastric pH
 - Interactions with medications like phosphate binders or antacids

B. Hepatic Disease:

- May impair **first-pass metabolism**, increasing the **bioavailability** of high-extraction drugs (e.g., propranolol, morphine)

Distribution:

A. Renal Disease:

- **Fluid overload** → Increases Volume of Distribution (Vd) of hydrophilic drugs (e.g., aminoglycosides)
- **Hypoalbuminemia or uremia** → Reduces plasma protein binding, increasing free (active) drug concentration

B. Hepatic Disease:

- **Hypoalbuminemia** → Reduces protein binding of acidic drugs (e.g., phenytoin, warfarin)
- Increases the free fraction, potentially enhancing drug effects or toxicity

Metabolism:

A. Renal Disease:

- **Downregulation** of some non-renal metabolic pathways in CKD
- **Uremic toxins** may inhibit liver enzymes (e.g., cytochrome P450 system)

B. Hepatic Disease:

- The liver is responsible for **Phase I** (oxidation, reduction, hydrolysis) and **Phase II** (conjugation) metabolism
- Impaired liver function leads to:
 - Decreased metabolic clearance

- Increased half-life
- Accumulation of parent drug or active metabolites

Elimination:

1. Renal elimination:

- In renal impairment, drugs cleared through glomerular filtration, tubular secretion, or reabsorption will accumulate.
- Requires adjustment in dose or dosing interval.

2. Hepatic elimination:

- Hepatic insufficiency reduces biliary excretion of drugs and metabolites.
- Important for drugs like rifampin, erythromycin, and chlorpromazine.

Half-life ($t_{1/2}$):

- Increased in both renal and hepatic disease for many drugs due to decreased clearance.
- Prolonged half-life necessitates changes in dosing to avoid toxicity.

Therapeutic Drug Monitoring (TDM):

- Essential for drugs with a narrow therapeutic index and significant changes in PK parameters.
- Drugs often monitored: aminoglycosides, digoxin, phenytoin, lithium, vancomycin.

General Approach for Dosage Adjustment in Renal Disease

- Renal impairment significantly alters drug pharmacokinetics, especially drug clearance. Hence, **dose individualization** becomes essential.
- The goal is to maintain therapeutic drug levels without causing toxicity.

Steps for Dosage Adjustment:

1. Assess Renal Function:

- Estimate **glomerular filtration rate (GFR)** or **creatinine clearance (CrCl)** using formulas such as:
 - Cockcroft-Gault equation
 - MDRD (Modification of Diet in Renal Disease)
 - CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration)

2. Determine Drug Elimination Pathway:

- Check whether the drug is **primarily renally excreted** or metabolized by the **liver**.
- Drugs with >30% renal clearance typically require dose adjustment.

3. Check for Active or Toxic Metabolites:

- Some drugs are metabolized into active or toxic forms, which are renally excreted (e.g., meperidine → normeperidine).

4. Check the Therapeutic Index:

- Narrow therapeutic index drugs (e.g., digoxin, lithium) require closer monitoring and more precise adjustments.

5. Determine Dosage Adjustment Strategy:

- Two common approaches:
 - **Reduce the dose** while maintaining the same dosing interval (useful when reducing peak concentrations is critical).
 - **Extend the dosing interval** while using the same dose (preferred when maintaining peak levels is important).

6. Use Available Guidelines:

- Refer to **drug-specific renal dosing recommendations**, often found in product labels or clinical handbooks (e.g., Lexicomp, Micromedex).

7. Monitor Therapeutic Response and Adverse Effects:

- Adjust therapy based on clinical response and side effects.
- Employ **therapeutic drug monitoring (TDM)** when applicable.



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