

## RENAL IMPAIRMENT

### Definition/Introduction

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The effects of many drugs are altered in renal impairment, particularly when a drug is renally cleared. Drug doses should be altered based on the predicted reduction in the clearance of the drug. Patient factors, such as the degree of renal disease and patient size, also influence the decision to adjust drug doses. In addition, drug factors, including the drug excretion and the therapeutic index, must be considered when adjusting doses. Accurate estimation of renal function is crucial for determining appropriate doses of renally excreted drugs.

Renal disease can alter drug concentrations and effects in the body, occasionally reducing effects but more commonly escalating their effects and thus causing potential toxicity. Most of these changes are predictable and may be prevented by altering drug doses in accordance with established guidelines.

Renal disease primarily affects drug dosing in 3 ways:

- Patient susceptibility: Patients with renal impairment may be more vulnerable to a specific drug effect.
- Pharmacodynamic change: The effect of a drug may be increased or decreased in patients with renal disease.
- Pharmacokinetic changes: When given at usual doses, some drugs have higher steady-state concentrations in patients with renal impairment.

Chronic kidney disease (CKD) is a type of kidney disorder characterized by a gradual decline in kidney function that occurs over several months to years.<sup>[1]</sup> Although various organs contribute to drug metabolism and excretion, the liver is the primary site for metabolism, and the kidneys are primarily responsible for excretion.

CKD is defined as a glomerular filtration rate (GFR) lower than 60 mL/min or albumin higher than 30 mg/g of creatinine, accompanied by abnormalities of kidney structure or function for more than 3 months. End-stage renal disease is a GFR of less than 15 mL/min.

Renal impairment modifies the effects of many medications, occasionally diminishing them but more typically enhancing or even multiplying them, thus leading to accumulation and potential toxicity. Many of these alterations can be and should be predicted and subsequently alleviated by adjusting drug doses.

In summary, the medication dose should be decreased equivalently to the calculated reduction of drug clearance.

### Issues of Concern

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CKD is classified into 6 stages. Determining whether a patient has renal insufficiency (CKD stages 2 through 5) and identifying the specific stage are crucial because the kidneys excrete almost half of all drugs or their metabolites, and 30% of all adverse effects of medication are attributed to either a renal cause or a renal effect.<sup>[2]</sup> CKD affects a significant proportion of the general population, especially hospitalized patients. According to the NHANES study, the prevalence of renal insufficiency with a GFR below 60 mL/min is 11% to 13%, and about 20% of hospitalized patients have impaired renal function.

In patients with renal impairment, the dosing of renally cleared drugs has to be adjusted based on the patient's actual GFR. In the past, this adjustment was made using the Cockcroft-Gault equation or by

measuring creatinine clearance.[4] Previously, the Modification of Diet in Renal Disease (MDRD) formula was also used. However, the Chronic Kidney Disease-Epidemiology Collaborative Group (CKD-EPI) creatinine-based formula has largely replaced these older methods.

The CKD-EPI task force has also developed complex equations incorporating serum creatinine and cystatin C, using a population comprising healthy individuals and CKD patients, which are preferred when estimating GFRs in multi-ethnic populations due to their reduced bias.[5] A recent review by Inker et al presented new equations using cystatin C and creatinine without race, demonstrating an improved correlation between measured and calculated GFR. These complex equations can be found in this study and supplementary materials.[6]

The use of race as a qualitative factor to estimate muscle mass was previously supported, but the trend is toward removing race from GFR calculations. The current CKD-EPI formulas have gone through several iterations. Although some experts may prefer eGFR equations using cystatin or both cystatin and creatinine, in practice, cystatin is not widely measured. Therefore, the National Kidney Foundation (NKF) and the American Society of Nephrology (ASN) Task Force recommend using the CKD-EPI creatinine-based equation.[7] This formula uses serum creatinine, age, and constant values. For estimated GFR, this formula has been adopted by most major laboratories, including national laboratories.

The GFR is estimated using various formulas, and it is calculated as follows:

- The Cockcroft-Gault formula

$$\text{GFR} = [(140 - \text{age}) \times \text{weight}] / [(72 \times \text{SCr}) \times 0.85 \text{ (if female)}]$$

- The MDRD equation

$$186 \times (\text{SCr}/88.4) \times (\text{Age}) \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$$

- CKD-EPI equation

$$\text{eGFR} = 142 \times \min(\text{SCr}/\kappa, 1)^{\alpha} \times \max(\text{SCr}/\kappa, 1)^{-1.200} \times 0.9938^{\text{Age}} \times 1.012 \text{ (if female)}$$

Abbreviations/units SCr is serum creatinine in mg/dL  $\kappa = 0.7$  for females and  $0.9$  for males  $\alpha = -0.329$  for females and  $-0.411$  for males  $\min =$  the minimum of  $S/\kappa$  or  $1$ , and  $\max =$  the maximum of  $S/\kappa$  or  $1$

### Classification of CKD Based on GFR

- Stage 1: GFR 120 to 90 mL/min (GFR is normal, but mild abnormalities, such as proteinuria, indicate possible underlying renal pathology)
- Stage 2: GFR 89 to 60 mL/min (mild renal insufficiency)
- Stage 3a: GFR 59 to 45 mL/min (intermediate renal insufficiency)
- Stage 3b: GFR 44 to 30 mL/min (moderate renal insufficiency)
- Stage 4: GFR 29 to 15 mL/min (severe renal insufficiency)
- Stage 5: GFR 14 to 0 mL/min (preterminal, requires renal replacement therapy)

The units of drug dosing are typically expressed as the amount of drug administered per unit of time. Dose adjustment is typically crude for most drugs in many circumstances, such as doubling or halving doses. In most cases, having the means to establish when the drug dose should be doubled or halved is crucial, whereas a 20% alteration in dose is typically impractical and unnecessary. However, there are many drugs for which minor changes in dose or concentration may cause a significant effect, commonly called a narrow therapeutic index. The therapeutic index is calculated using the following formula:

- The therapeutic index = minimum toxic dose / minimum effective dose

## Clinical Significance

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Factors and conditions that may worsen the renal injury and thus should be either avoided or resolved include the following:

- Nephrotoxic drugs, such as nonsteroidal anti-inflammatory drugs, aminoglycosides, and iodinated contrast
- Uncontrolled diabetes
- Systemic hypertension
- Proteinuria
- Dehydration
- Smoking
- Hyperlipidemia
- Hyperphosphatemia

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## Nursing, Allied Health, and Interprofessional Team Interventions

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Based on several studies, 34% to 53% of the drugs requiring adjustment were not considered in physicians' instructions.[8][9] There are various explanations for the inadequacy of medication dose regulation. The most frequent reason is that physicians often underestimate the impact of mild and intermediate renal insufficiency or that they have inadequate knowledge of the medications that require dose adjustment in renal insufficiency. Although the serum creatinine level is a widely used value in everyday practice, this is a late biomarker of decreased renal function (rising only after significant loss of renal function), thus leading to underestimating renal impairment, especially among older patients.

Another possible explanation is that physicians do not calculate the creatinine clearance using one of the three existing formulas due to insufficient time, which leads to underestimating the necessity of adjusting medication dosage.[10] The Food and Drug Administration and European Medicines Agency have particular guidelines about pharmacokinetics regarding patients with impaired renal function that should be followed when developing new drugs.[11][12] Physicians should consider the potential adverse effects, drug interactions, and treatment failures or discontinuations due to nephrotoxicity before administering any drug.

Effective communication between physicians, pharmacists, and nurses is essential for safe and appropriate drug administration in patients with renal impairment.