THE KIDNEYS for Intensivists

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What a Laboratory Technician Should Know About the Kidney

Kidney Functions:

- **Blood Filtration**: The kidney filters blood through the **glomerulus**, removing waste and excess fluids.
- **Regulation**: Maintains balance of **electrolytes**, **fluids**, and **acid-base** in the body.
- **Hormonal Production**: Secretes **erythropoietin** for red blood cell production and regulates blood pressure through **renin**.

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What a Laboratory Technician Should Know About the Kidney

Important Laboratory Tests:

1. **Serum Creatinine (SCr)**:
   1. Indicator of kidney function. Used to calculate **Creatinine Clearance (CrCl)** and **eGFR** (estimated glomerular filtration rate).
2. **Blood Urea Nitrogen (BUN)**:
   1. Measures **urea** produced by the liver and filtered by the kidneys. The **BUN/SCr ratio** helps distinguish between **prerenal** and **intrinsic** causes of kidney failure.
3. **Electrolytes**:
   1. The kidney regulates levels of **sodium**, **potassium**, **chloride**, and **bicarbonate** in the blood.
4. **Proteinuria/Albuminuria**:
   1. The presence of proteins in urine may indicate kidney damage.

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What a Laboratory Technician Should Know About the Kidney

Collection Procedures:

- **Urine Collection**:
  - Tests such as **Creatinine Clearance** measurement require accurate urine collection, often over a 24-hour period.
- **Proper Sample Handling**:
  - Correct handling and dosing of blood and urine samples are crucial for obtaining reliable results.

Relevant Conditions and Diseases:

- **Chronic Kidney Disease (CKD)**:
  - Progressive loss of kidney function. Technicians must monitor biomarkers like SCr and BUN to assess disease progression.
- **Acute Kidney Injury (AKI)**:
  - Sudden decline in kidney function. Requires careful evaluation of SCr and electrolyte balance.

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Why a intensivist physician ask so many kidney test for the patients?

1. Monitoring for Acute Kidney Injury (AKI)
•**AKI is common in critically ill patients**, often due to sepsis, dehydration, shock, or drug toxicity. Early detection through tests like **serum creatinine (SCr)** and **blood urea nitrogen (BUN)** can help guide treatment and prevent worsening of kidney function.

2. Fluid and Electrolyte Balance
•The kidneys are responsible for regulating the body's **fluid levels** and maintaining **electrolyte balance** (e.g., sodium, potassium, chloride). **Electrolyte imbalances** can lead to life-threatening complications such as cardiac arrhythmias, and intensivists need to monitor these closely in ICU patients.

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Why a intensivist physician ask so many kidney test for the patients?

3. Drug Dosing and Toxicity
•Many drugs used in the ICU are excreted through the kidneys, and **dosing adjustments** are necessary in patients with impaired renal function. Kidney function tests like **creatinine clearance (CrCl)** or **eGFR** help ensure **safe dosing** of medications, particularly nephrotoxic drugs (e.g., certain antibiotics, diuretics).

4. Assessing Hydration and Perfusion
•**Volume status** is critical in the ICU. Tests like **BUN**, **SCr**, and **urine output** help the intensivist assess whether a patient is adequately perfused (i.e., receiving enough blood flow to the kidneys) or if they are at risk of dehydration or overhydration.

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Why an intensivist physician ask so many kidney test for the patients?

5. Prognostic Indicator
•Kidney function tests can provide important prognostic information. **Worsening kidney function** in critically ill patients is associated with higher morbidity and mortality, making it essential to monitor kidney health regularly.

6. Renal Replacement Therapy Decisions
•If a patient's kidney function deteriorates significantly, the intensivist may need to decide if **dialysis or continuous renal replacement therapy (CRRT)** is required. Frequent kidney tests guide this decision.

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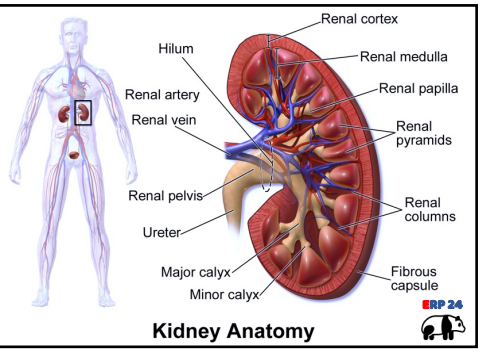

Kidney Anatomy

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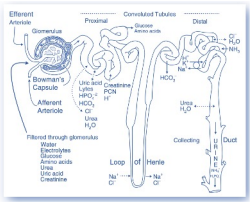
The Nephron: The Functional Unit of the Kidney

•**Overview**: Each kidney contains approximately 1 million nephrons, which are the key functional units of the kidneys.

•**Major Components**:
- **Glomerulus**: Filters blood; allows substances <40,000 daltons to pass through (e.g., ions, small molecules).
- **Proximal Tubule**: Reabsorbs water, solutes like sodium, glucose, bicarbonate, and amino acids.
- **Loop of Henle**: Further reabsorbs sodium, chloride, water, and magnesium.
- **Distal Tubule**: Regulates sodium, potassium, bicarbonate, phosphate, and hydrogen excretion.
- **Collecting Duct**: Regulates water reabsorption influenced by antidiuretic hormone (ADH).



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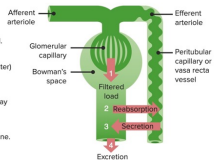
Filtration and Kidney Function

•**Glomerular Filtration**:
- Blood reaches the glomerulus via the afferent arteriole, filtering about 20% of plasma.
- The glomerular filtration rate (GFR) is around 125 mL/min, filtering 180 L/day, with 1.5 L excreted as urine.

•**Tubular Secretion & Reabsorption**:
- Secretion occurs mainly in the proximal tubule (organic acid and cation transport systems).
- Reabsorption from the distal tubule to systemic circulation occurs via peritubular vasculature.

•**Renal Blood Flow**:
- Kidneys receive 20% of cardiac output (~1.2 L/min).
- GFR is crucial for assessing kidney function (plasma clearance of creatinine).

1. **Filtration**
Plasma is filtered from blood.
2. **Reabsorption**
Useful materials (solutes, water) are reabsorbed.
3. **Secretion**
Metabolic waste products may be secreted, too.
4. **Excretion**
Remainder is excreted as urine.



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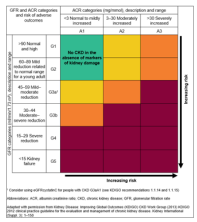
Definition and Classification of Chronic Kidney Disease (CKD)

Definition: CKD is defined as a **GFR <60 mL/min/1.73 m² for >3 months**, indicating significant kidney damage or reduced kidney function.

Nature or Cause of Abnormality:
•**Structural**: Includes conditions like polycystic kidney disease, hydronephrosis.
•**Functional**: Based on changes in kidney function such as urinary sediment or renal tubular disorders.

Based on GFR:
•G1: Normal or high (>90 mL/min)
•G2: Mild reduction (60-89 mL/min)
•G3a: Mild to moderate reduction (45-59 mL/min)
•G3b: Moderate to severe reduction (30-44 mL/min)
•G4: Severe reduction (15-29 mL/min)
•G5: Kidney failure (<15 mL/min)



Albuminuria Categories:
•**A1**: Normal to mildly increased (ACR <30 mg/g)
•**A2**: Moderately increased (ACR 30-300 mg/g)
•**A3**: Severely increased (ACR >300 mg/g)

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Prognosis & Risk

Based on markers and GFR, CKD risk is categorized from **low risk** (no markers) to **very high risk**.

GL in the **KDIGO 2012 CKD Guidelines**. GFR <60 mL/min/1.73 m2 for greater than three months.

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Assessment of Kidney Function

Direct GFR Measurement:

- **Markers**: Inulin, iothalamate (most accurate but not routinely used due to cost and complexity).

Key Characteristics

1.Biologically Inert: Inulin is not metabolized by the body, making it ideal for tracking how substances are filtered.
2.Freely Filtered by the Glomerulus: It passes through the glomerulus without being reabsorbed, secreted, or metabolized in the renal tubules.
3.Reliable GFR Measurement: Inulin's clearance from the bloodstream into the urine directly reflects glomerular filtration, providing a highly accurate estimate of kidney function.

Why Inulin?

•**Accuracy**: Since it is not affected by renal tubular processes, inulin offers an exact measurement of GFR.

•**Use in Research**: Inulin is often used in clinical research and specific diagnostic settings, though not routinely in practice due to cost and complexity compared to simpler methods like creatinine clearance or eGFR estimations.

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Assessment of Kidney Function

Timed 24-hour Urine Creatinine (UCr):
•Used only in critical cases.
•**Challenges**: Prone to collection errors and difficult to perform.

Key Characteristics:
1.Measures Creatinine Excretion: Collects all urine over 24 hours to measure the total amount of creatinine excreted by the kidneys.
2.Used to Estimate GFR: Provides an estimate of kidney function based on creatinine clearance (CrCl).
3.Required for Critical Cases
4.Challenges:

1. **Collection Errors**: inaccurate results.

When?

Donald Van Slyke, an American biochemist who significantly advanced the understanding of kidney function and clinical chemistry. He contributed to developing methods for measuring renal function, including creatinine clearance.

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Assessment of Kidney Function

Estimated Creatinine Clearance (CrCl):

•**Cockcroft-Gault Equation**: "Gold standard" for drug dosing.

Key Characteristics:
•**Purpose**: Estimates creatinine clearance (CrCl) as a surrogate for **glomerular filtration rate (GFR)**.
•**Cockcroft-Gault Equation**:

- Developed to estimate CrCl using **age, weight, serum creatinine**, and **gender**.
- Used to adjust **medication doses** for patients with impaired renal function.

•**"Gold Standard" for Drug Dosing**: Provides a practical method to adjust dosing

Discovery:

•**Developed in 1976** by **Dr. Henry Cockcroft** and **Dr. Matthew Gault**.

•**Historical Importance**: Prior to eGFR equations, it was the primary method for estimating kidney function and remains widely used in drug dosing protocols.

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Assessment of Kidney Function

eGFR Estimation:
•Initially validated with **MDRD Equation**, now replaced by the **CKD-EPI Equation (2009)**.
•**Cystatin C**: Emerging as an alternative for GFR estimation in both children and adults.

Key Characteristics:
1.eGFR (Estimated Glomerular Filtration Rate):

1. A calculation used to estimate kidney function based on **serum creatinine**, age, gender, and race.
2. Provides a non-invasive, reliable method to monitor and stage **Chronic Kidney Disease (CKD)**.

2.MDRD Equation (Modification of Diet in Renal Disease):

1. Initially validated in 1999 to estimate GFR, particularly in CKD patients.
2. Less accurate at higher GFR values (>60 mL/min/1.73 m^2).

NEW

1.CKD-EPI Equation (2009):

1. Developed to improve accuracy, especially at **normal to mildly reduced GFR** levels.
2. Now recommended over the MDRD equation for routine use in clinical practice.

2.Cystatin C:

1. An emerging marker for estimating GFR, especially useful in **children** and **adults**.
2. Less influenced by muscle mass, potentially offering a more accurate reflection of kidney function.

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Exogenous Markers – Inulin Clearance

Inulin Clearance: Gold Standard for Measuring GFR

Normal Range:
- **Men**: 125 ± 15 mL/min/m²
- **Women**: 110 ± 15 mL/min/m²

•**Key Characteristics**:
- **Inulin**: A fructose polysaccharide (MW: 5200 daltons), **inert and not protein-bound**.
- **Freely Filtered by Glomerulus**: No reabsorption, secretion, or metabolism in the kidneys.
- Considered the **"gold standard"** for measuring **GFR** in **adults and older children** due to its precise reflection of kidney filtration.

Limitations:

•**Invasive Procedure**: Requires **intravenous administration** of inulin.

•**Special Analytical Methods**: Not widely available due to the complexity and cost of testing.

•**Challenges in Neonates/Younger Children**: Accurate urine flow rates can be difficult to measure in these populations.

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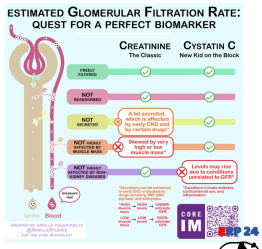
Endogenous Markers – Cystatin C

Cystatin C: A Key Endogenous Marker for GFR Estimation

•**Normal Reference Range**:
- **Men**: 0.6–1.52 mg/L
- **Women**: 0.57–1.45 mg/L

•**Key Characteristics**:
- **Protease Inhibitor**: Produced at a steady rate by all nucleated cells.
- **Filtered by Glomerulus**: Not reabsorbed or secreted by the kidney.
- **Unaffected by Diet or Muscle Mass**: Provides a more consistent reflection of kidney function than serum creatinine (SCr).



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Endogenous Markers – Cystatin C

Cystatin C: A Key Endogenous Marker for GFR Estimation

Clinical Relevance:

•**More Sensitive than SCr**: Better at tracking changes in kidney function, especially when combined with other factors (SCr, age, sex, race).
•**Use in eGFR Equations**: Cystatin C is increasingly incorporated into GFR estimation equations, especially for pediatric patients.
•**Certification and Standardization**: The use of certified cystatin C reference materials (ERM-DA471/FCC) is rapidly evolving, with NKDEP supporting its use in eGFR equations.
•**CVD Link**: Elevated cystatin C levels are associated with increased risk of **cardiovascular disease mortality**.

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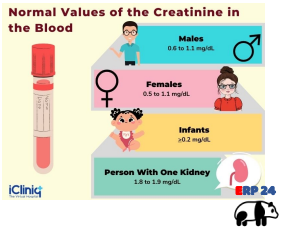
Endogenous Markers – Serum Creatinine (SCr)

Key Marker of Kidney Function

Normal Range:
•**Adults**: 0.6–1.2 mg/dL (53–106 mmol/L)
•**Young Children**: 0.2–0.7 mg/dL (18–62 mmol/L)

Key Characteristics:
•**Creatinine**: A nonprotein, nitrogenous compound derived from **creatine**.
•**Produced in Muscle**: A byproduct of **creatine phosphate** metabolism, a key energy source for muscle action.
•**Constant Production**: Creatinine is produced at a constant rate (2% of body creatine), dependent on muscle mass.



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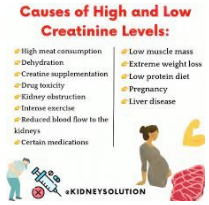
Endogenous Markers – Serum Creatinine (SCr)

Clinical Relevance:

•**Steady-State Indicator**: In healthy individuals, **creatinine production equals excretion**, resulting in stable serum levels.

•**Not Sole Indicator**: Factors like **muscle mass**, **sex**, **age**, **race**, medications, and diet affect SCr, making it an imperfect standalone marker of kidney function.

•**Delayed Response in Acute Changes**: Acute declines in GFR may not immediately reflect in SCr due to the time needed to reach a new steady-state.



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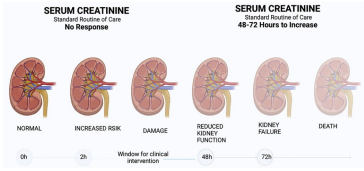
Endogenous Markers – Serum Creatinine (SCr)

Limitations:

Normal SCr Doesn't Ensure Normal Function: A normal SCr value does not always correspond to normal GFR.

For example, the same SCr (1.5 mg/dL) in different individuals (e.g., a 45-year-old male vs. a 78-year-old female) can indicate varying levels of kidney function.



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Serum Creatinine (SCr) and GFR Interpretation

Key Insights for Clinicians:

•**Increased SCr Almost Always Reflects Decreased GFR**:
- If muscle mass is stable, an elevated SCr is a reliable indicator of reduced kidney function.

•**Normal SCr Does Not Guarantee Normal GFR**:
- **Aging Effect**: Both **muscle mass** and **renal function** decline with age, keeping SCr in the normal range even when GFR is reduced.
- **Clinical Implication**: Do not rely solely on SCr as an index of renal function.

Special Considerations:

•**Cirrhosis**:
- **Overestimation of Renal Function**: Low SCr can occur in cirrhotic patients due to decreased hepatic synthesis of creatine, leading to lower creatinine production.
- **Recommended Action**: Use **24-hour creatinine clearance (CrCl)** in these patients for accurate renal assessment.
- **Hyperbilirubinemia**: Elevated bilirubin levels may interfere with SCr assays, contributing to falsely low SCr readings.

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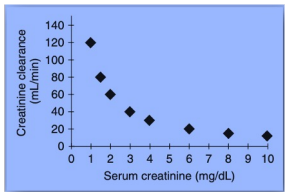
Inverse relationship between SCr and CrCl



Relatively small changes in SCr at lower levels represent significant change in kidney function as assessed by CrCl.

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Historical Methods of SCr Measurement

•**Alkaline Picrate Assay (Jaffe Method)**:
- Most common method, but prone to interference from noncreatinine chromogens (e.g., uric acid, glucose, ketones).
- Can lead to **falsely elevated SCr** and underestimation of kidney function.
- **Examples**:
  - Glucose increase of 100 mg/dL can raise SCr by 0.5 mg/dL.
  - Diabetic ketoacidosis (DKA) can result in falsely elevated SCr due to high serum ketones.

•**Other Methods**:
- **Inorganic Enzymatic Methods** and **High-Pressure Liquid Chromatography** (HPLC).

Measurement Issues:
•**Falsely Elevated SCr**: Due to noncreatinine chromogens, especially in conditions like DKA or fasting (elevated acetoacetate).
•**Falsely Low SCr**: Elevated bilirubin can interfere, leading to underreporting of SCr.
•**Overestimation of GFR**: At low GFR, creatinine secretion can overestimate GFR by up to 50%.

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Urea (Blood Urea Nitrogen - BUN)

Normal Range:
•**8–23 mg/dL** (2.9–8.2 mmol/L)

Key Characteristics:

•**BUN**: Measures the concentration of nitrogen (as urea) in the **serum**, not in red blood cells.
•**Dependent on Multiple Factors**:
- **Urea Production** (in the liver)
- **Glomerular Filtration**
- **Tubular Reabsorption**

•**Not a Standalone Marker for Kidney Function**: BUN must be interpreted alongside other clinical and laboratory data.

Clinical Uses:
•Assess and monitor:
- **Hydration status**
- **Renal function**
- **Protein tolerance** and **catabolism**

•**Predict Risk of Uremic Syndrome**: BUN levels >100 mg/dL (35.7 mmol/L) indicate a high risk in patients with severe renal failure.

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Elevated and Decreased BUN – Clinical Implications

Elevated BUN

•**Causes of Increased Urea Production**:
- **High-protein diet** (including amino acid infusions)
- **Upper GI bleeding**
- **Corticosteroids**, tetracyclines, or drugs with antianabolic effects.

•**Reabsorption Factors**:
- Urea reabsorption is inversely related to **urine flow rate**.
- Slower urine flow = More urea reabsorbed into surrounding capillaries.
- Reabsorption parallels **sodium, chloride**, and **water** reabsorption (e.g., in volume depletion).

•**Associated Conditions**:
- **Congestive heart failure** (reduced renal blood flow despite increased volume).
- **Low blood pressure** leading to decreased GFR and urine flow.
- **Azotemia** (abnormally high BUN) in renal failure.

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Elevated and Decreased BUN – Clinical Implications

Decreased BUN

Causes:
- **Malnutrition** or **liver damage** (inability to synthesize urea).
- **Intravascular fluid overload** can dilute BUN initially, but conditions like **congestive heart failure**, **renal failure**, or **nephrotic syndrome** may lead to increased BUN due to reduced effective circulating volume.

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BUN to SCr Ratio – Diagnostic Insights

BUN
Ratio:
•Simultaneous measurement of **BUN** and **serum creatinine (SCr)** provides valuable information for assessing **kidney function**, especially in **acute kidney injury**.

Key Diagnostic Observations:
•**BUN**
•**> 20:1**:
- Suggests **prerenal causes** of acute kidney injury, such as **volume depletion**.
- Due to increased **urea reabsorption** (with water) under decreased renal perfusion, while creatinine is not reabsorbed.

•**BUN**
•**10:1 to 20:1**:
- Suggests **intrinsic kidney damage**.

Clinical Relevance:

•**Elevated Ratio > 20:1** is important when both BUN and SCr are **above normal limits**.
- Example: SCr >1.2 mg/dL, BUN >23 mg/dL.

•If both BUN and SCr are within **normal ranges**, a high ratio is not clinically significant.
- Example: SCr = 0.8 mg/dL, BUN = 20 mg/dL.

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Measurement of Creatinine Clearance (CrCl)

24-Hour Urine Collection for CrCl:

•**Best Used**: In clinical situations with **unstable serum creatinine (SCr)**, particularly during acute changes in kidney function.

Key Considerations:
•**Not Superior** to CrCl estimates from equations (e.g., Cockcroft-Gault, MDRD) according to the **National Kidney Foundation**.

When to Use 24-Hour CrCl:

1. **Patients Starting Dialysis**
2. **Acute Kidney Injury (AKI)** or **Acute Renal Failure** in hospitalized patients.
3. **Comorbid Conditions** affecting kidney function.
4. **Evaluation of Dietary Intake**: Especially in vegetarians or those with extreme dietary habits.
5. Patients with **extremes in muscle mass**:
   1. **Athletes** taking creatine supplements.
   2. **Vegetarians**, **quadriplegics/paraplegics**, or those with **amputations**.

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Interpreting Creatinine Clearance (CrCl) with Renal Parameters

Common Clinical Uses of CrCl and SCr:

•**Assessing kidney function** in patients with **Chronic Kidney Disease (CKD)**.
•**Monitoring drug therapy** effects on slowing CKD progression.
•**Monitoring nephrotoxic drug** effects.
•**Adjusting drug dosages** for renally eliminated medications.

Key Insights:
•**Inverse Relationship**: The relationship between **SCr** and **CrCl** is **geometric**, not linear.
- **CrCl may significantly decline** before SCr rises above the normal range.
- Early stages of kidney dysfunction may not be detected by **SCr** alone.

Clinical Relevance:

•**SCr is not a sensitive indicator** of early kidney dysfunction.

•Significant reductions in **CrCl** can occur before SCr reflects impaired renal function.

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Calculating Creatinine Clearance (CrCl) from a Timed Urine

Collection

Urine Collection Periods:
•CrCl is commonly calculated using a **12-hour or 24-hour urine collection**.
•**Normal Creatinine Excretion**:
- **Men**: 20–28 mg/kg/24 hr
- **Women**: 15–21 mg/kg/24 hr
- **Children**: 15 + (0.5 × age) mg/kg/24 hr

•**CrCl (mL/min)** = $\frac{UCr \times V}{SCr \times T} \times \frac{1.73}{BSA}$

- **UCr** = Urine creatinine concentration (mg/dL)
- **V** = Volume of urine produced (mL)
- **SCr** = Serum creatinine concentration (mg/dL)
- **T** = Time of collection interval (minutes)
- **BSA** = Body Surface Area (m^2)

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Calculating Creatinine Clearance (CrCl) from a Timed Urine

BSA Calculation:

- **Dubois and Dubois:**

$$BSA(m^2) = 0.20247 \times \text{Height}^{0.725} \times \text{Weight}^{0.425}$$

- **Mosteller Equation:**

$$BSA(m^2) = \sqrt{\frac{\text{Height(cm)} \times \text{Weight(kg)}}{3600}}$$

Clinical Relevance:

•**Adjusting CrCl for BSA (1.73 m²)**: Allows comparison with standard CrCl ranges and is important for patients with significantly larger or smaller body sizes.

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Estimation of Creatinine Clearance (CrCl)

Clinical Use:

•**Cockcroft-Gault Equation**: Traditionally used for dosing medications excreted via the kidneys.

•**Caution**: With standardized creatinine reporting, calculated CrCl may be **5–20% higher**, potentially leading to discrepancies in dose adjustments based on older assays.

Cockcroft-Gault Formula:

$$CrCl = \frac{(140 - \text{Age}) \times \text{Weight(kg)}}{72 \times SCr} \times 0.85\,(\text{if female})$$

- **Variables:** Age, total body weight (TBW), serum creatinine (SCr).

Considerations:

•**Weight Selection**:
- Ideal Body Weight (IBW) vs. Total Body Weight (TBW) vs. Adjusted Body Weight (ABW) – No consensus on the best approach for CrCl estimation.

•**Adjustments**: Rounding SCr to 1.0 mg/dL or using adjusted/lean body weight may not be clinically validated.

•**Use in Unstable Renal Function**: The Cockcroft-Gault equation should be used **cautiously** in patients with unstable kidney function.

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Estimation of GFR – MDRD Equation

Purpose:
•Developed to identify patients at risk for complications from **Chronic Kidney Disease (CKD)**.

MDRD Equation:
•Provides an **estimated GFR (eGFR)** based on **Iothalamate reference values**.
•Initially useful for identifying **CKD stages**, but **no longer recommended** for routine use due to limitations.

Key Limitations:
•**Underestimates GFR** in patients with eGFR >60 mL/min/1.73 m², leading to potential **overdiagnosis of CKD**.
•Vulnerable to **errors** in patients at age extremes or with **low muscle mass** (e.g., cachexia).
•Should be used **cautiously** in patients with **unstable renal function**.
Current Recommendations:
•**KDIGO Guidelines**: Suggest using **cystatin C** or **direct CrCl measurement** when SCr values are unreliable or in patients with eGFR >60 mL/min/1.73 m².

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Medication Safety in Patients with Kidney Disease

Physician Role:

•**Optimize medication use** in patients with **acute kidney disease (AKD)** and **chronic kidney disease (CKD)**.
•Evaluate the need for:

- **Dose adjustments**
- **Extended dosing intervals**
- **Discontinuation** or **avoidance** of nephrotoxic drugs

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AGENTS	CAUTIONARY NOTES
1. Antihypertensives/cardiac medications	
RAAS antagonists (ACE IIi, ARBs, aldosterone antagonists, direct renin inhibitors)	• Avoid in people with suspected functional renal artery stenosis • Start at lower dose in people with GFR <45 mL/min/1.73 m² • Assess GFR and measure serum potassium within 1 wk of starting or following any dose escalation • Temporarily suspend during intercurrent illness, planned IV radiocontrast administration, bowel preparation prior to colonoscopy, or prior to major surgery • Do not routinely discontinue in people with GFR <30 mL/min/1.73 m² as they remain nephroprotective
β-blockers	• Reduce dose by 50% in people with GFR <30 mL/min/1.73 m²
Digoxin	• Reduce dose based on plasma concentrations
2. Analgesics	
NSAIDs	• Avoid in people with GFR <30 mL/min/1.73 m² • Prolonged therapy is not recommended in people with GFR <60 mL/min/1.73 m² • Should not be used in people taking lithium • Avoid in people taking RAAS blocking agents
Opioids	• Reduce dose when GFR <60 mL/min/1.73 m² • Use with caution in people with GFR <15 mL/min/1.73 m²
3. Antimicrobials	
Penicillin	• Risk of crystalluria when GFR <15 mL/min/1.73 m² with high doses • Neurotoxicity with benzylpenicillin when GFR <15 mL/min/1.73 m² with high doses (maximum 6 g/day)
Aminoglycosides	• Reduce dose and increase dosage interval when GFR <60 mL/min/1.73 m² • Monitor serum levels (trough and peak) • Avoid concomitant ototoxic agents such as furosemide
Macrolides	• Reduce dose by 50% when GFR <30 mL/min/1.73 m²
Fluoroquinolones	• Reduce dose by 50% when GFR <15 mL/min/1.73 m²
Tetracyclines	• Reduce dose when GFR <45 mL/min/1.73 m², can exacerbate uremia
Antifungals	• Avoid amphotericin unless no alternative when GFR <60 mL/min/1.73 m² • Reduce maintenance dose of fluconazole by 50% when GFR <45 mL/min/1.73 m² • Reduce dose of flucytosine when GFR <60 mL/min/1.73 m²

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AGENTS	CAUTIONARY NOTES
4. Hypoglycemics	
Sulfonylureas	• Avoid agents that are mainly renally excreted (e.g., glyburide/glibenclamide) • Other agents that are mainly metabolized in the liver may need reduced dose when GFR <30 mL/min/1.73 m² (e.g., gliclazide, glipizide)
Insulin	• Partly renally excreted and may need reduced dose when GFR <30 mL/min/1.73 m²
Metformin	• Suggest avoiding when GFR <30 mL/min/1.73 m², but consider risk-benefit if GFR is stable • Review use when GFR <45 mL/min/1.73 m² • Probably safe when GFR ≥45 mL/min/1.73 m² • Suspend in people who become acutely unwell
5. Lipid-lowering	
Statins	• No increase in toxicity for simvastatin dosed at 20 mg per day or simvastatin 20 mg/ezetimide 10-mg combinations per day in people with GFR <30 mL/min/1.73 m² or on dialysis[2] • Other trials of statins in people with GFR <15 mL/min/1.73 m² or on dialysis also showed no excess toxicity
Fenofibrate	• Increases SCr by approximately 0.13 mg/dL (12 μmol/L)
6. Chemotherapeutic	
Cisplatin	• Reduce dose when GFR <60 mL/min/1.73 m² • Avoid when GFR <30 mL/min/1.73 m²
Melphalan	• Reduce dose when GFR <60 mL/min/1.73 m²
Methotrexate	• Reduce dose when GFR <60 mL/min/1.73 m² • Avoid if possible when GFR <15 mL/min/1.73 m²
7. Anticoagulants	
Low-molecular-weight heparins	• Halve the dose when GFR <30 mL/min/1.73 m² • Consider switch to conventional heparin or alternatively monitor plasma anti-factor Xa in those at high risk for bleeding
Warfarin	• Increased risk of bleeding when GFR <30 mL/min/1.73 m² • Use lower doses and monitor closely when GFR <30 mL/min/1.73 m²
8. Miscellaneous	
Lithium	• Nephrotoxic and may cause renal tubular dysfunction with prolonged use even at therapeutic levels • Monitor GFR, electrolytes, and lithium levels monthly or more frequently if the dose changes or the patient is acutely unwell • Avoid using concomitant NSAIDs • Maintain hydration during intercurrent illness • Risk-benefit of drug in specific situation must be weighed

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