

Kidney dysfunction



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Functions of the kidneys

- Water and electrolyte homeostasis
- Excretion in the urine of waste products of metabolism
- Excretion of chemicals/drugs
- Hormone production: renin, EPO, active form of vitamin D (1,25 dihydroxyvitamin D₃)
- Gluconeogenesis – during starvation
- Acid-base balance: HCO₃⁻ & H⁺



Clinical assessment of renal function

- 5-15 % pts in ICU
- Changes in renal function directly affect drug disposition

GFR (Glomerular Filtration Rate) – standard measure

RBF – 20 % of CO

AUTOREGULATION



Clinical assessment of renal function

1. Renal Blood Flow 1-1.2l/min

- Research studies – PAH Clearance
- Alternatives
 - Selective arteriography
 - Doppler ultrasonography
 - External radionuclide scanning



Clinical assessment of renal function

Renal Blood Flow

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Almost totally cleared
from arterial plasma by
filtration & secretion



Clinical assessment of renal function

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PAH CI approximates RPF



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To document renal perfusion



Renal Blood Flow

Clinical correlates

- **Optimize CO & ECF**
- **Low dose/renal dose dopamine infusion (<3 $\mu\text{g}/\text{kg}/\text{min}$) → renal vasodilatation**
 - Beneficial effects not documented in
 - NaCl depletion
 - Volume depletion
 - Infusion for 24-36 h



Renal Blood Flow

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- Fenoldopam – selective D1 agonist
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 - \rightarrow \uparrow urine/Na output



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 - \curvearrowright \uparrow urine/Na output
- **PG – anecdotal evidence**

Potential vasodilator



2. GFR

Renal clearance

= Volume of plasma completely cleared of the substance by the kidneys per unit of time

Glucose

- Normally zero

Inulin

- Freely filtered and not acted upon

Gentamicin Cl

PAH (para-aminohippuric acid)

- Effective renal plasma flow

Creatinine

Urea



2. GFR

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Creatinine
Urea

Freely filtered, minimally absorbed by the tubules

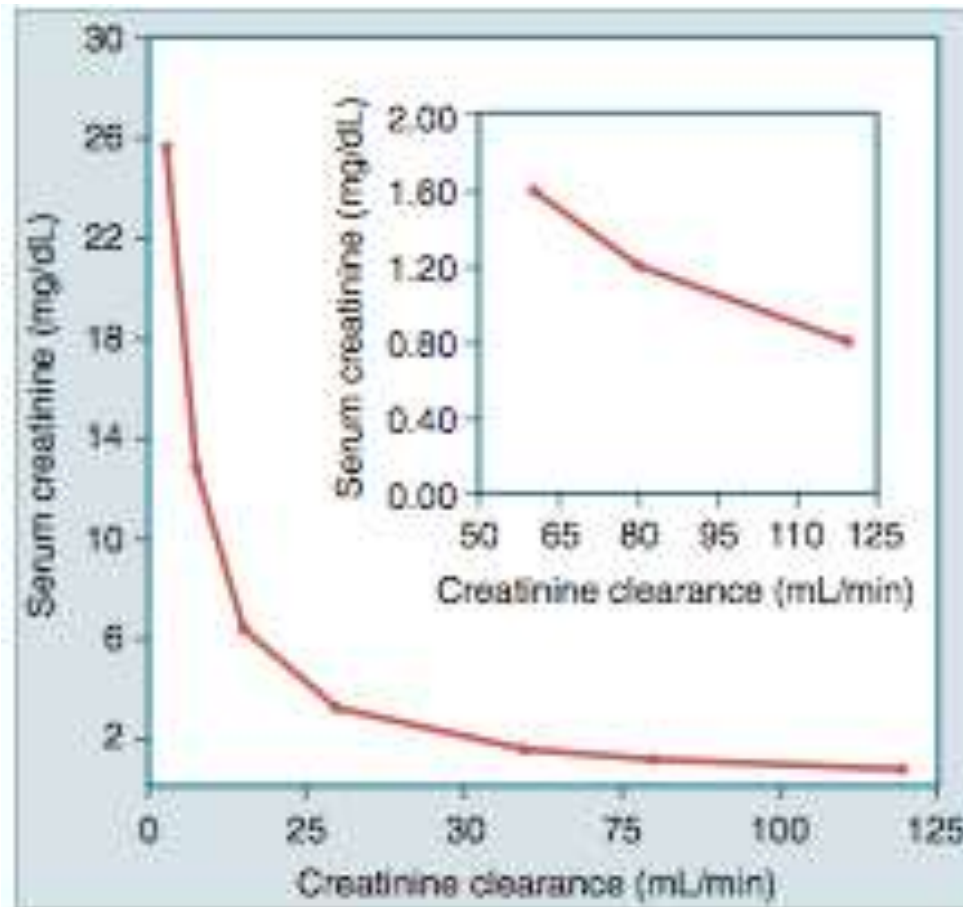
!overestimates GFR due to secretion

Underestimates GFR

Serum creatinine

Insensitive marker of early change

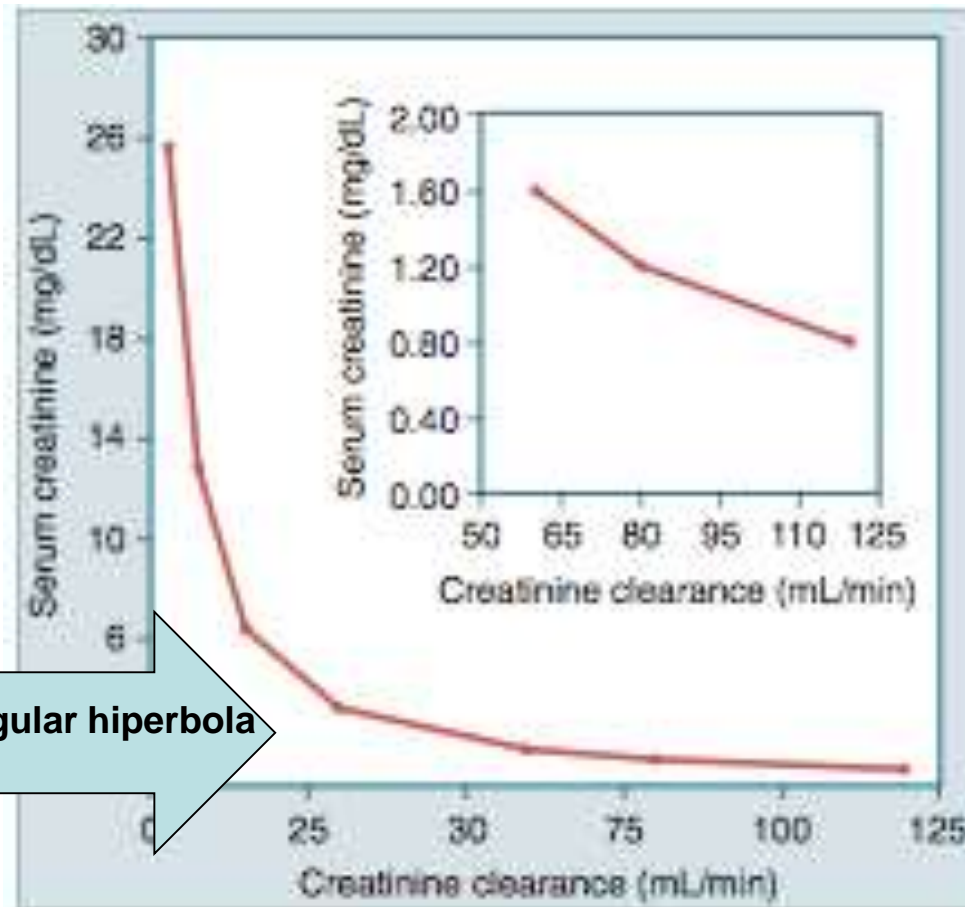
Close estimate of GFR in steady state



Serum creatinine

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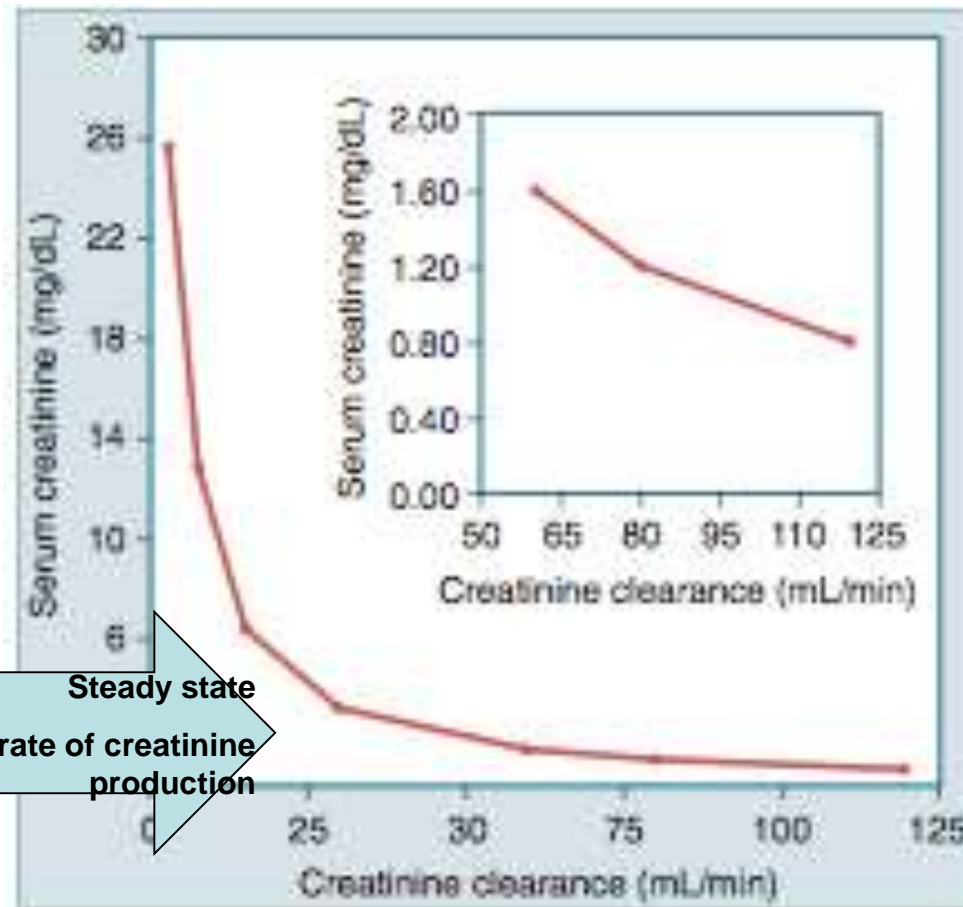
Rectangular hiperbola



Serum creatinine

Insensitive marker of early change

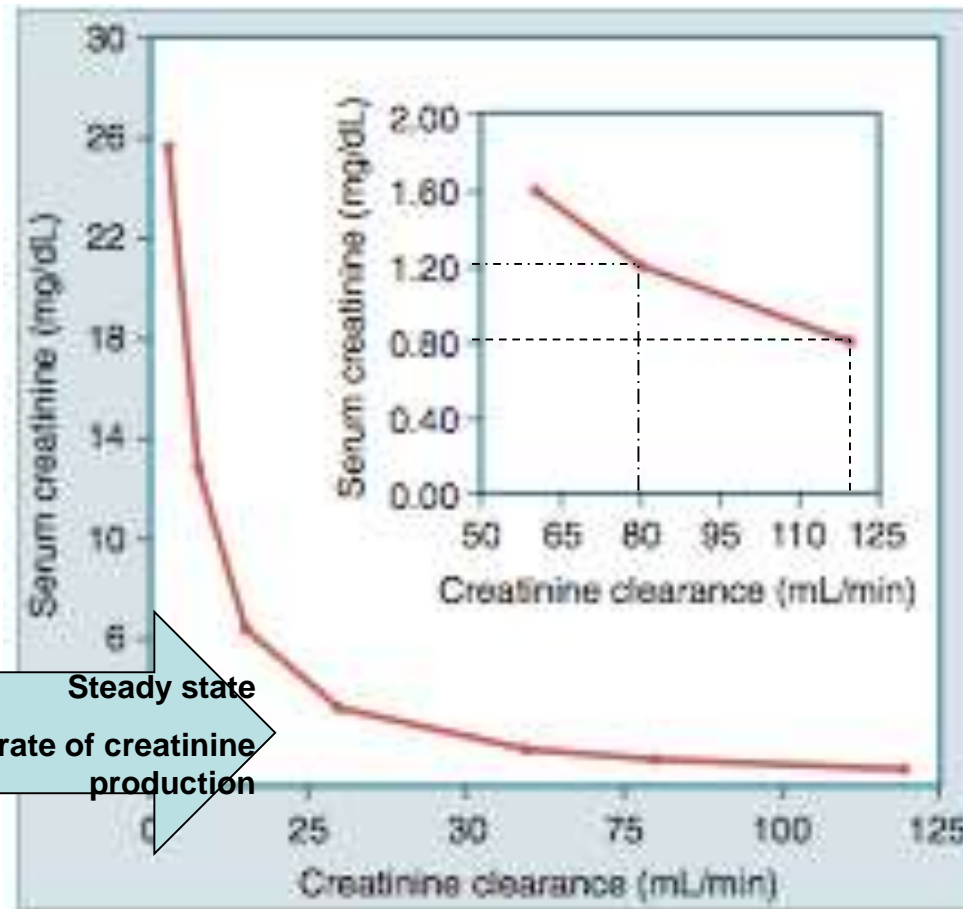
Close estimate of GFR in steady state



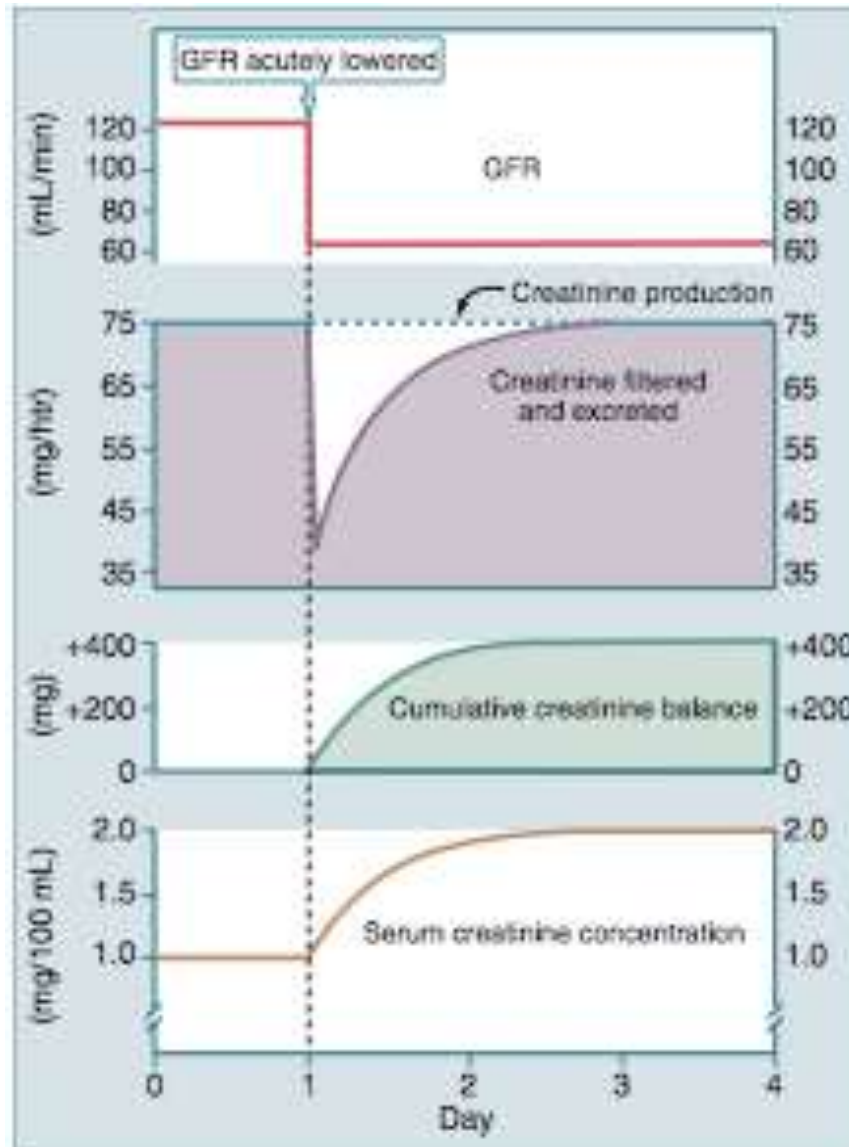
Serum creatinine

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Close estimate of GFR in steady state



Serum creatinine



Creatinine clearance estimate

- **Cockcroft-Gault**

$C_{Cr} = [(140 - \text{age}) \times \text{lean w in kg}] / S_{Cr} \times 72$ for men

$\times 0.85$ for women

- **MDRD (Modification of Diet in Renal Disease)**

- Clinical laboratories

- Underestimation of GFR at high values

- $GFR = 186 \times [S_{Cr}]^{-0.999} \times [\text{age}]^{-0.203} \times [0.742$
if patient is female] $\times [1.212$ if patient is black]



Creatinine clearance estimate

- **Cockcroft-Gault** ↓creatinine generation:
 $C_{Cr} = \frac{1.73}{\text{men}} \times 0.85$
 - **MDRD**
Disease
 - CKD
 - Uremia
 - Glomerulonephritis
 - Ageing
 - Hepatic diseases
 - Excessive muscle wasting
 - Severe muscular atrophy or dystrophy
 - Hyperthyroidism
 - Paralysis
 - Chronic glucocorticoid therapy
- black]



Serum urea nitrogen **SUN = BUN**

- Variable production – absorbed Hb from the GI tract in bleeding
 - Freely filtered, but reabsorbed
- ⑩ ↑ by
- Tetracyclines - **antianabolic effect**
 - Glucocorticoids
 - Severe illness/trauma
- } **Endogenous hipercatabolism, hyperfeeding**
- Marked dispropotion in the elevation of SUN compared with S_{Cr}



Serum urea nitrogen **SUN + BUN**

- Variable production
- ⑩ ↑ by
 - Tetracyclines
 - Glucocorticoids
 - Severe illness/trauma
- Marked disproportion in the elevation of SUN compared with S_{Cr}

Less accurate than S_{Cr} for GFR



Na balance and ECF

- 140-142 mmol/L
- ECF 20% TBW, 1/3 total body water
- $FE_{Na} = U_{Na}/S_{Na} \times S_{Cr}/U_{Cr}$
- Diuretics



Acute kidney injury (AKI)

Abrupt decrease in GFR → accumulation of nitrogenous waste products

+

Inability to maintain fluid and electrolyte homeostasis

Medulla = low blood flow and low oxygen tension (10 mmHg) **very susceptible to ischemic injury**



Prerenal causes

- Reduction in renal perfusion without cellular injury
- Reversible process if the underlying cause is corrected
 - Decreased blood volume
 - Vomiting
 - Dehydration
 - Hemorrhage
 - Reduction in the effective arterial blood flow
 - Congestive heart failure
 - Cirrhosis
 - Drugs that interfere with autoregulatory ability
 - NSAIDs
 - ACE



Prerenal causes

Activation of RAA system & ↑ activity of renal adrenergic system

- Proximal reabsorption of Na
- Distal reabsorption of Na (aldosterone)

70% of community-acquired cases of AKI

40% of hospital-acquired cases of AKI

Prerenal causes should be excluded in all cases of AKI



Postrenal causes

- Bilateral
 - Unilateral (single kidney)
- } Obstruction of urine flow
- Incidence 3-25% AKI
 - Community >>>> ICU
 - Renal
 - Crystal deposition (ethylene glycol ingestion)
 - Uric acid nephropathy (tumor lysis syndrome)
 - Extrarenal
 - Prostatic disease
 - Pelvic malignancy
 - Retroperitoneal disorders



Intrarenal causes

Classified according to anatomic location

- Glomerulus
- Tubule
- Vasculature
- Interstitium

Glomerulonephritis/vasculitis

Renal failure

Active urine sediment (red cells, red cells casts)

Acute interstitial nephritis

Pyuria & white cells casts

Drug related (ATB, NSAIDs)

Recovery hastened by short course of steroids: 60-80 mg prednisone for 10 days



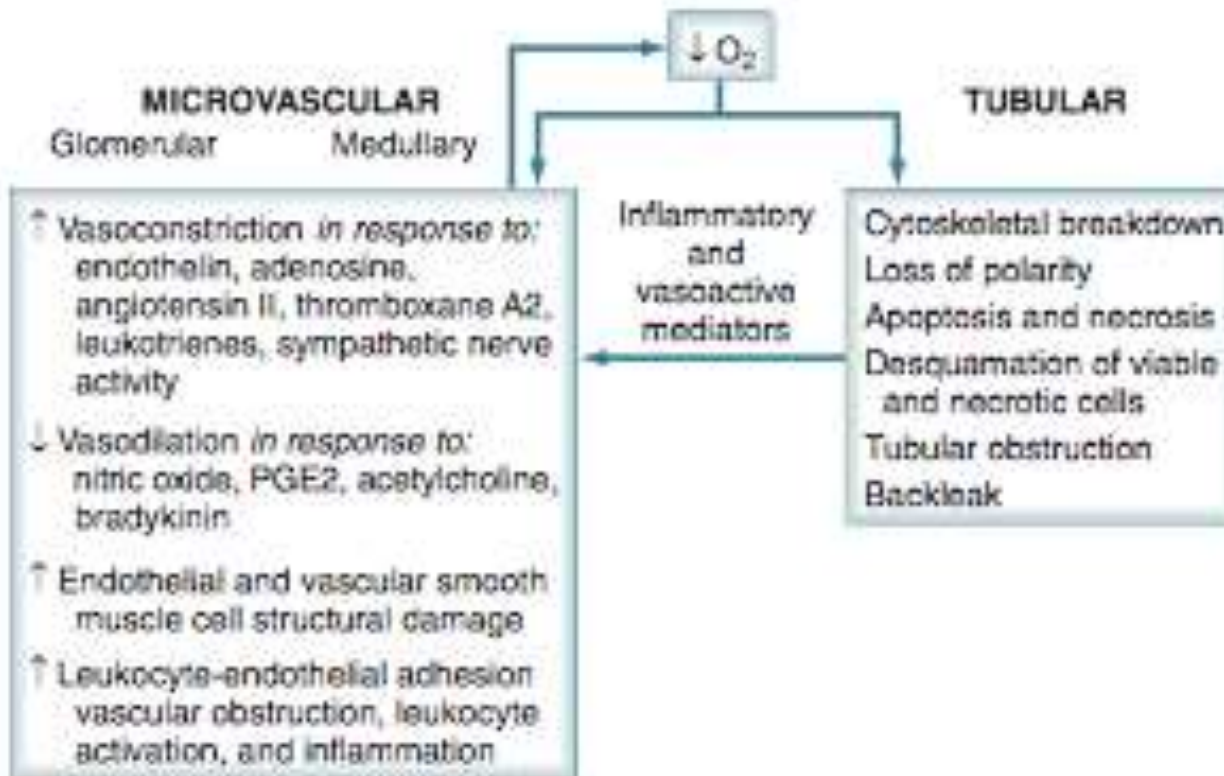
Intrarenal causes

ATN (acute tubular necrosis)

ICU most common form of AKI

Tubular & vascular injury

PATHOPHYSIOLOGY OF ISCHEMIC ACUTE KIDNEY INJURY



Laboratory and microscopic findings in prerenal azotemia and ATN

Laboratory test	Prerenal azotemia	Acute Tubular Necrosis
Urine osmolality (mOsm/kg H ₂ O)	>500	<4400
Urine sodium (mEq/L)	<20	>40
Urine/plasma creatinine ratio	>40 (>15)	<20
FE _{Na} (%)	<1	>2 (exception rhabdomyolysis, myoglobinuria, contrast mediated AKI, sepsis)
Urinary sediment	Normal, occasional hyaline cast	Renal tubular epithelial cells, granular and muddy brown casts
FE _{Urea} for those on diuretics	< 35% No distinction between transient and persistent AKI	

Epidemiology

- RIFLE criteria – 1/3 of ICU pts (manifestation of multiorgan failure syndrome)
 - Multifactorial cause (sepsis)
 - Mortality 40-80%
- Risk factors for developing AKI
 - Age > 65 years
 - Infection on admission
 - Cardiovascular failure
 - Cirrhosis
 - Respiratory failure
 - Chronic heart failure
 - Lymphoma or leukemia



Epidemiology

- Risk factors for mortality
 - Higher severity index score
 - Age > 65 years
 - Male gender
 - Oliguric acute renal failure
 - Sepsis
 - Nonrenal organ failure
 - Thrombocytopenia
 - Mechanical ventilation
 - Prior compromised health status
- Low serum creatinine with poor outcome (reflective of poor nutritional status)
- AKI causes mortality vs marker of severely ill patients



Definition

- Lack of a standard one
- AKIN – Acute Kidney Injury Network
- ADQI – Acute Dialysis Quality Initiative
 - Develop consensus & EB guidelines
 - RIFLE criteria
 - R - Risk
 - I - Injury
 - F - Failure
 - L - Loss (> 4 weeks)
 - E - End stage renal failure (> 3 months)

Better account for small changes (+ anyone who receives acute RRT irrespective of their preceding S_{Cr} increase or urine output)



New staging

RIFLE stages	RIFLE SCr increase	RIFLE and AKIN urine output	AKIN SCr increase	AKIN stages
Risk	≥150% to 200%	<0.5 ml/kg/h for > 6 h	≥0.3 mg/dL or ≥150% to 200%	1
Injury	>200% to 300%	<0.5 ml/kg/h for > 12 h	>200% to 300%	2
Failure	>300% or Scr > 4mg/dL or ↓ GFR by 75%	<0.3 ml/kg/h for > 24 h or anuria ≥ 12 h	>300% or Acute RRT	3

From baseline to 48 h

Biomarkers under investigation

- Serum cystatin C
- Urinary IL-18
- Tubular enzymes
 - Intestinal form of alkaline phosphatase
 - N-acetyl- α -glucosaminidase
 - Alanine aminopeptidase
- **Neutrophil gelatinase – associated lipocalin (NGAL)**
- Kidney injury molecule 1 (KIM-1)



Treatment

- **No role for dopamine**
- **Diuretics have not been shown to prevent or ameliorate AKI. They can be used in the initial management of AKI to facilitate fluid balance and treat hyperkalemia or hypercalcemia, but their use should not delay commencing RRT when deemed clinically necessary**
 - Oliguric → nonoliguric (better outcome)**
No reduction in the need for RRT or mortality.
- **Nesiritide (BNP) – on trial**



Hemodynamic management

- **EGDT may reverse adverse hemodynamics before tissue injury occurs → better outcome**
- **Recognition of pseudo-ARDS (noncardiogenic pulmonary edema in the absence of evidence of decreased pulmonary compliance)**
- **Fluid management to improve organ perfusion
Type of fluid???**
- **Ne vs dopamine**
- **Vasopressin?**
- **Tight glycemic control? < 150 mg/dL**



Nutritional support

- ⑩ ↑ protein catabolism (insulin resistance)
- Enteral nutrition recommended
- Caloric supplementation 20-30 kcal/kg/d
 - Lipids
 - Immuno-enhancing
- No role for protein restriction
 - 0.8-1.2 g/kg/d AKI without need for RRT
 - 1-1.5 g/kg/d AKI on RRT



Renal Replacement Therapy (RRT)

- Early initiation is beneficial
- Clinical context + trends of laboratory tests + metabolic indicators
- IHD – intermittent hemodialysis
- SLED – slow low-efficiency dialysis
- CRRT – continuous RRT
- PD – peritoneal dialysis



RRT potential indications

- Nonobstructive oliguria (urine output <200 mL/12 h) or anuria
- Severe acidemia
- Azotemia (blood urea nitrogen >80 mg/dL)
- Hyperkalemia (K^+ >6.5 mmol/L) **IHD**
- Uremia (encephalopathy, pericarditis, neuropathy, myopathy)
- Severe dysnatremia (Na^+ >160 or <115 mmol/L)
- Hyperthermia (temperature >39.5° C)
- Clinically significant organ edema (especially lung)
- Drug overdose with dialyzable toxin
- Coagulopathy requiring large amounts of blood products in a patient at risk for adult respiratory distress syndrome

Note: Any one of these indications is sufficient to consider initiating renal replacement therapy. Two of these indications make renal replacement therapy desirable.



Contrast induced nephropathy (CIN)

= acute kidney function impairment within 72 h of intravascular injection of iodinated radiocontrast media in the absence of other ethiology

= 25% ↑ S_{Cr} or
absolute increase of 0.5 mg/dL S_{Cr}

Incidence: 1-30%

Pathogenesis: direct toxic injury to renal tubular cells and medullary ischemic injury (subcorticomedullary congestion)



CIN – Risk factors

- **Preexisting kidney function ($C_{Cr} < 47$ ml/min)**
- **Type of imaging procedure**
- **Diabetes (nephropathy)**

- **Age > 75 years**
- **Periprocedure volume depletion**
- **Heart failure**
- **Hypotension**
- **Cirrhosis**
- **Proteinuria**
- **Coadministration of nephrotoxins**



Clinical features, diagnosis, prognosis

- Generally asymptomatic
- Peaks at 3 d, returns to baseline in 10 d
- **Other potential causes must be ruled out**
- < 1% require dialysis (13-50% permanent)
- ??? Casualy linked to early death and adverse cardiovascular events



CIN prevention

1. **Assess risk/benefit of the proposed intervention**
2. **Assess kidney function – eGFR**
3. **Modify correctable risk factors & hold nephrotoxins**
4. **High risk pts, IA contrast – low osmolar or iso-osmolar contrast medium**
5. **Identify patients at risk**
6. **Use the lowest dose of appropriate contrast medium**



CIN prevention

7. Correct hypovolemia

Stop diuretics

Consider IV fluids (type & quantity ???)

0.9% saline vs isotonic sodium bicarbonate

Begin at least 1 h prior to contrast injection

Continue for at least 6 h (12h before & after – best supported)

3 m/kg/h x 1h followed by 1ml/kg/h

8. N-acetylcysteine (NAC) – higher doses & IA administration

1200 mg BID PO started Z-1, x 2 d

Emergent procedure:

- 1200 mg IV
- Followed by above 4 doses

9. Prophylactic RRT

