Critical Care Medicine

Volume - 2

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AKI : PART I

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Background

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- 1802 : William Heberden → Described acute kidney injury as Ischuria Renalis.
- 2004 : Bellom o et al → AKI (RIFLE criteria).
- AKIN criteria (2007).
- KDIGO criteria (2012).
- Acute kidney injury (AKI) : Syndrome characterized by a rapid deterioration of kidney function occurring within hours or days.

Classification :

- RIFLE : ADQI Group, 2004.
- AKIN : AKIN Network, 2007.
- KDIGO : KDIGO Group, 2012.

	RIFLE	AKIN	KDIGO
Diagnostic criteria			
		Increase in serum creatinine of ≥0.3 mg/dL or ≥50% within 48 hours OR Urine output of <0.5 mL/kg/hour for >6 hours	Increase in serum creatinine of ≥0.3 mg/dL within 48 hours or ≥50% within 7 days OR Urine output of <0.5 mL/kg/hour for >6 hours
Staging criteria			
Risk (RIFLE) or stage 1 (AKIN/KDIGO)	Increase in serum creatinine of 50 to 99% OR Urine output of <0.5 mL/kg/hour for 6 to 12 hours	Increase in serum creatinine of ≥0.3 mg/dL or 50 to 100% OR Urine output of <0.5 mL/kg/hour for 6 to 12 hours	Increase in serum creatinine of ≥0.3 mg/dL or 50 to 99% OR Urine output of <0.5 mL/kg/hour for 6 to 12 hours
Injury (RIFLE) or stage 2 (AKIN/KDIGO)	Increase in serum creatinine of 100 to 199% OR Urine output of <0.5 mL/kg/hour for 12 to 24 hours	Increase in serum creatinine of >100 to 200% OR Urine output of <0.5 mL/kg/hour for 12 to 24 hours	Increase in serum creatinine of 100 to 199% OR Urine output of <0.5 mL/kg/hour for 12 to 24 hours
Failure (RIFLE) or stage 3 (AKIN/KDIGO)	Increase in serum creatinine of ≥200% OR Increase in serum creatinine by >0.5 mg/dL to > 4.0 mg/dL OR Urine output of <0.3 mL/kg/hour for > 24 hours or anuria for >12 hours OR Initiation of renal replacement therapy	Increase in serum creatinine of >200% OR Increase in serum creatinine by > 0.5 mg/dL to ≥4.0 mg/dL OR Urine output of <0.3 mL/kg/hour for > 24 hours or anuria for > 12 hours OR Initiation of renal replacement therapy	Increase in serum creatinine of ≥200% OR Increase in serum of ≥0.3 mg/dL to ≥4.0 mg/dL OR Urine output of <0.3 mL/kg/hour for ≥24 hours or anuria for ≥12 hours OR Initiation of renal replacement therapy
Loss (RIFLE)	Need for renal replacement therapy for >4 weeks		
End stage (RIFLE)	Need for renal replacement therapy for >3 months		

KDIGO definition of acute kidney injury :

Stage	Creatinine criteria	Urine output criteria
1	Cr 1.5-1.9 times baseline, OR Cr increase > 0.3 mg/dL	< 0.5 ml/kg/hr × 6-12 hours
2	Cr 2-2.9x baseline	< 0.5 ml/kg/hr for > 12 hours
3	Cr > 3x baseline, OR Cr > 4 mg/dL, OR Initiation of dialysis	< 0.3 ml/kg/hr for > 24 hours, OR Anuria > 12 hours

Patients are staged based on the single most concerning feature.

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Pitfalls :

Shortcoming	Potential solution
1. Inability of S. Creat to detect changes at high GFR level	1. Sequential creatinine clearances (e.g, with urine collections of 2-8 h)
2. S. Creat is a late marker of decreased GFR	2. Biomarkers of kidney damage/cystatin C/more frequent measurement of S. Creat
3. Critical illness may confound diagnosis by creatinine criteria	3. Correction of S. Creat for fluid balance/cystatin C
4. Requirement for baseline S. Creat with different methods to handle missing baseline	4. Thorough search for baseline/reporting applied method in literature
5. S. Creat is a measure of function not of tissue damage and may miss subclinical AKI	5. Combining S. Creat with biomarkers of kidney damage
6. Urine output criteria are less frequently used, lack specificity, and may be too liberal	6. Consistent use of urine output criteria and definition of more stringent criteria
7. KDIGO definition does not provide insight into pathophysiology	7. Use of biomarkers that reflect different pathophysiological mechanisms
8. Absence of gold standard	8. No solution for the time being
9. Different criteria for similar stage may have different association with outcome	9. Consensus criteria for RRT initiation/detailed description of AKI criteria
10. KDIGO definition is unreliable for assessment of renal recovery	10. Use of cystatin C/assess recovery by S. Creat after a sufficient time from critical illness (ie, after correction of sarcopenia and fluid overload)

AKI Spectrum

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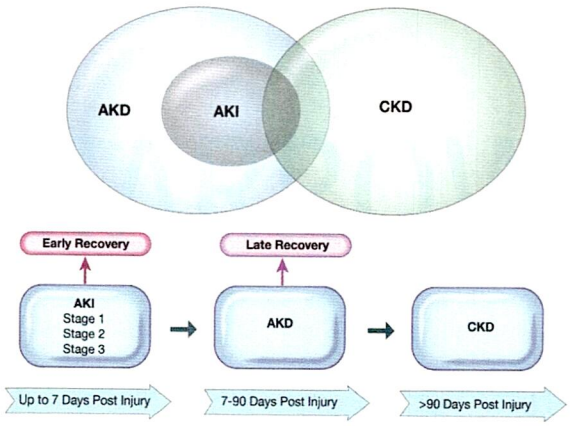
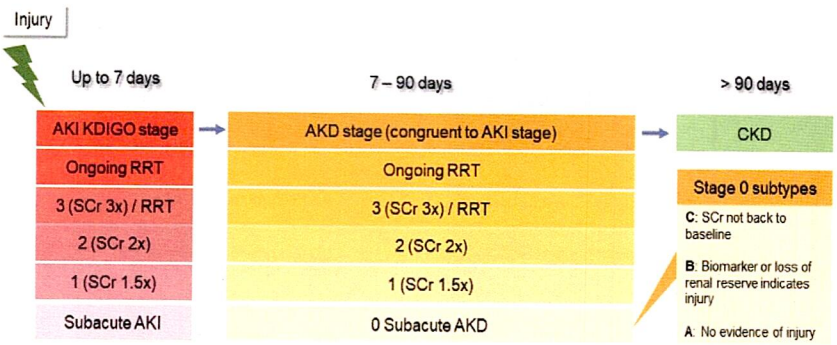


- Early recovery : S.creatinine/ urine output returning to baseline < 7 days.
- Rapid recovery : S.Cr / urine output returning to baseline < 48 hours.
- AKD :
  - Worse 1 year outcomes.
  - Recurrence of AKI.

AKI, AKD, CKD :



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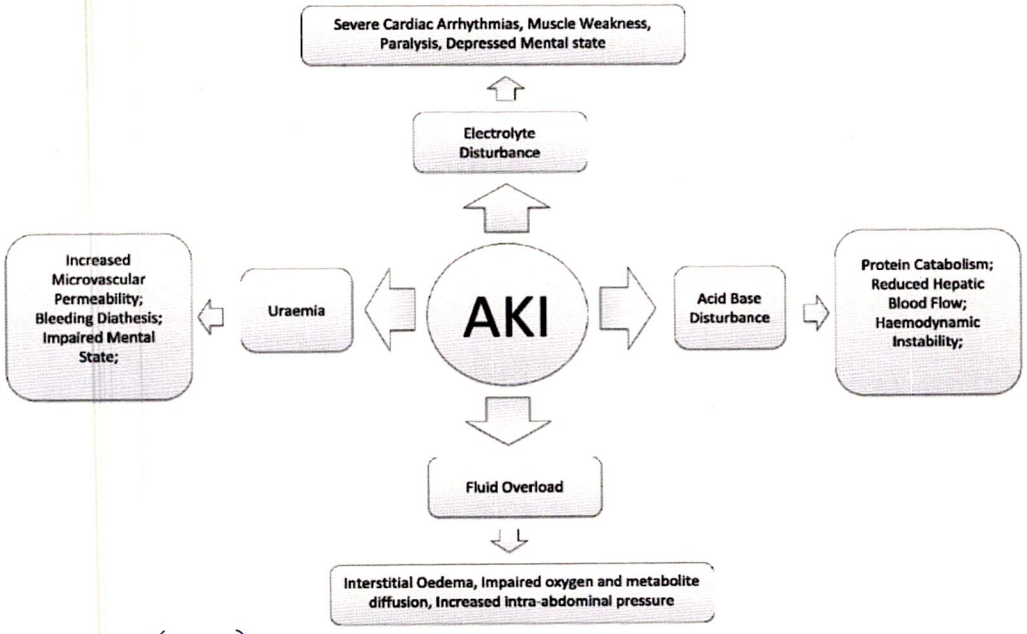
Incidence of AKI :

Incidence timing and outcome of AKI in critically ill patients.

- AKI incidence :
  - 35% : RIFLE.
  - 38% : AKIN.
  - 38% : KDIGO.
- 10-15% of AKI patients in ICU require renal replacement therapy (RRT).

Acute kidney injury → short term and long term effects :



- CKD : (14-20)%.
- Dialysis : (5-7)%.
- Coronary events : (10.3- 19.8)/1000 person year.
- Mortality : (30-40)%.

Risk factors for developing AKI in the ICU :

Non modifiable	Modifiable Risk factor

• Older age.
• Gender.
• Ethnicity.
• Comorbidity :
  • Hypertension.
  • Diabetes mellitus.
  • Chronic kidney disease.
  • Heart failure.
  • CAD & PAD.
  • COPD.
  • Obesity.
  • Malignancy.
	• Hypovolaemia.
	• Sepsis.
	• Choice of fluid.
	• Nephrotoxins.
	• Major surgery.
	• Trauma, including burn patients.
	• Critical illness.
	• Anemia.
	• Emergency procedures.
	• Radiologic Contrast Media.
	• COVID-19.

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Causes of AKI

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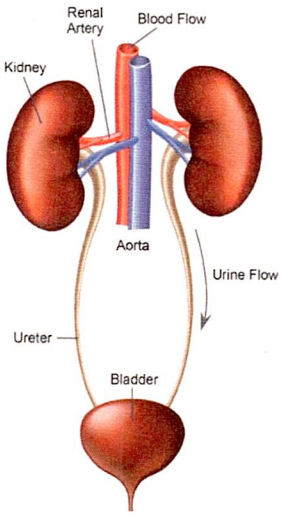
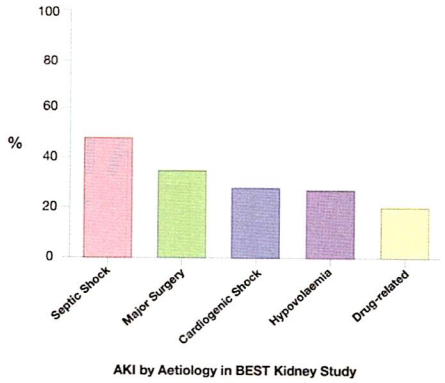
1. Prerenal : Sudden and severe reduction in blood pressure (shock) of interruption of blood flow to the kindeys from severe injury or illness.
    - Blood loss.
    - Dehydration.
    - Heart failure.
    - Sepsis.
    - Vascular occlusion.



2. Intrinsic Renal : Direct injury to the kidneys by inflammation, drugs, toxins, infection, or reduced blood supply.
    - Acute tubular necrosis :
        - Drugs.
        - Toxins.
        - Prolonged hypotension.
    - Glomerulonephritis
    - Acute tubular necrosis :
        - Drugs.
        - Toxins.
        - Autoimmune disease..
        - Infection.
    - Small-vessel vasculitis.
3. Postrenal : Sudden obstruction of urine flow due to enlarged prostate, kidney stones, bladder injury or tumor.
    - Benign prostatic hyperplasia.
    - Cervical cancer.
    - Meatal stenosis/phimosis.
    - Retroperitoneal fibrosis.
    - Prostate cancer.
    - Urinary calculi.

BEST study :

- 6647 patients in ICU.
- 19.2% developed AKI.



AKI by Aetiology in BEST Kidney Study

Pathology of AKI in the ICU :

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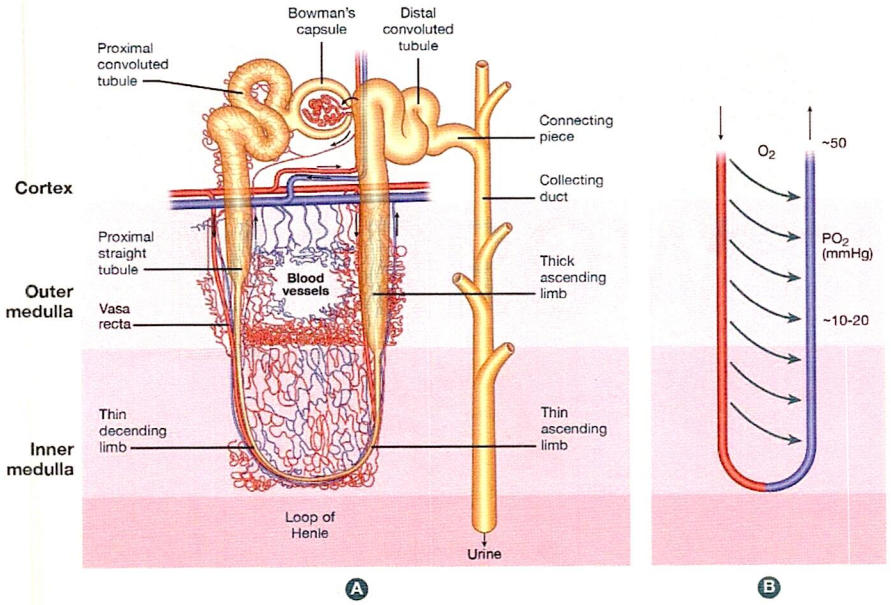

Septic AKI

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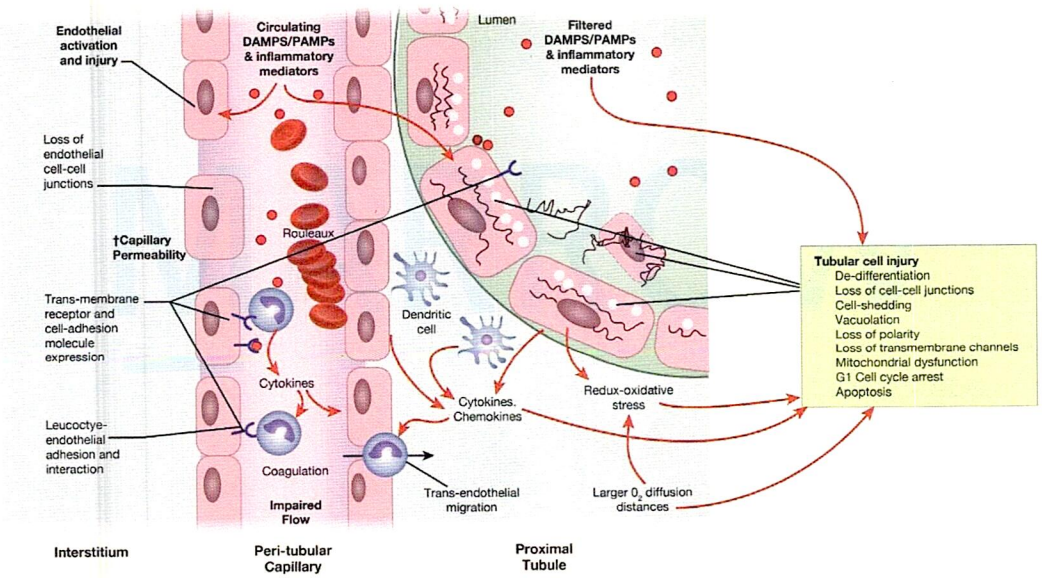
- Syndrome characterized by presence of sepsis and AKI definition.
- Incidence : >40% patient develop AKI.
- RRT: 30%.
- Mortality : 40%.
- Attributable mortality : 10%.

Pathophysiology of septic AKI :



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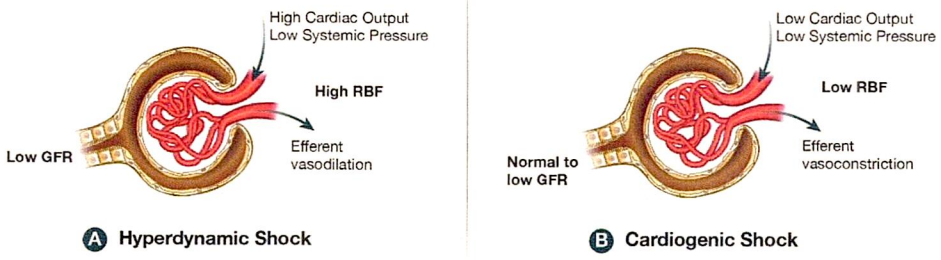
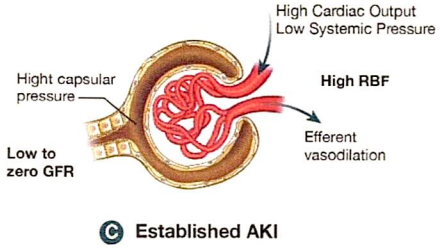
Effect on GFR :





Contrast Assoc AKI (CA-AKI) :

- Rise in SCr ≥ 0.5 mg/dl (44mmol/l) or a 25% increase from baseline value, assessed at 48 hours after a radiological procedure.
- Mechanism :
  - Direct tubular toxicity.
  - Intra renal vasoconstriction.
- Incidence :
  - Normal patients : 1-2%.
  - Patients with risk factors : upto 25%.
    - Pre existing renal dysfunction.
    - Diabetes.
    - LV dysfunction.
    - Concurrent nephrotoxic medications.
  - 3.3% (if SCr> 0.5mg/dl).
  - 10.2% (if SCr> 25% baseline).
  - 10.5% (if GFR<25% baseline).

Retrospective study :

Incidence & outcome of contrast-associated acute kidney injury assessed with (RIFLE) criteria in critically ill patients of medical & surgical intensive care units :

- Incidence of CI-AKI was 15.5%.
- 55.8% had pre-existing kidney injury.
- CA-AKI patients were divided into risk (31%), injury (31%), and failure (38%).
- Dialysis : 7% patient.

- Recovery rate of AKI was 17% at the time of hospital discharge.
- Higher APACHE II scores were associated with a higher risk of CA-AKI.

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Risk factors :

Definite	Conflicting
• Pre-existing kidney disease • Diabetes, hypertension, CHF • Advanced age • Volume depletion • Hemodynamic instability • Nephrotoxic medications • Large volume or high osmolality contrast agent	• ACE-I and ARBs • Renal transplantation • Multiple myeloma • Female • Cirrhosis

Prediction of CI-AKI after PCI mehran risk model, JACC,2004 :

Risk factors	Integer score (calculate)
Hypotension	5
IABP	5
CHF	5
Age > 75 years	4
Anemia	3
Diabetes	3
Contrast-media volume	1 per 100 ml
SCr > 1.5 mg/dl (> 132.6 µmol/l) or eGFR < 60 ml/min per 1.73 m^2	4 2 for 40-60 4 for 20-39 6 for <20

Note: Low risk: cumulative score < 5; High risk: cumulative score > 16.

7.5% for low [<5] and 57.3% for high [>16]

Preventive measures :

- Reduced dose of contrast medium.
- Isotonic saline.
- Isotonic bicarbonate solution.
- NAC.
- Diuretics.
- Statins.
- Theophylline.
- Fenoldopam.

(Diuretics, Statins, Theophylline, Fenoldopam) — No role

Contrast medium :

- Dose : < 100 ml.
- Gms of iodine/EGFR (<1=3%, >1%= 25%),
- Maximum dose : (5gm/kg) / SCr,
- Route : IV preferred over arterial.

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Ionicity	Osmolality mosm/kg H_2O	Relative Osmolality	Examples
Ionic monomer	1500-1900	High	Diatrizoate, iothalamate
Ionic dimer	600	Low	Ioxaglate
Nonionic monomer	500-700	Low	Iohexol,iopamidol,iomeprol
Nonionic dimer	290-320	Iso	Iodixanol,iotrolan

Saline :

- NS preferred over 45% DNS.
- 1 hr before & upto 6 hrs after administration.
- At least 100ml/hr urine output.
- Rate : (1-2)ml/kg/hr infusion.

NaHCO3 :

- Isotonic solution of $NaHCO_3$: 850 cc of D5 + 150 cc of 8.4 % $NaHCO_3$.

NAC :

- Controversial benefit.
- Oral route preferred : Tolerable and inexpensive.
- ACC/AHA guidelines do not recommend.
- KDIGO : Suggest oral administration.
- Low dose : 600 mg bd for 2 days.

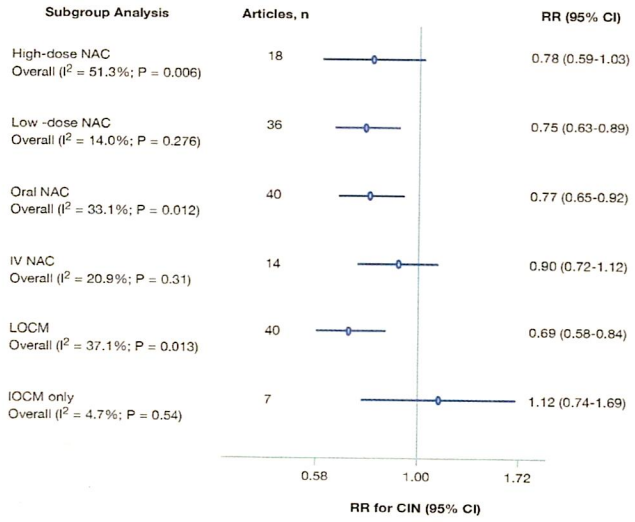
Preserve trial :

- Comparison of NS, $NaHCO_3$, NAC & Placebo.
- Result : No outcome benefits.

Effectiveness of Prevention Strategies for Contrast-Induced Nephropathy :

Pooled group	Studies, n	Pooled RR for CIN (95% CI)
High-dose NAC	18	0.78 (0.59-1.03)
IA administration	16	0.78 (0.55-1.12)
IV administration	2	0.55 (0.12-2.62)
Low-dose NAC	35	0.75 (0.63-0.89)
IA administration	30	0.77 (0.66-0.91)
IV administration	5	0.62 (0.18-2.10)
Oral NAC	40	0.77 (0.65-0.92)
IV NAC	14	0.90 (0.72-1.12)
NAC when LOCM are used	40	0.69 (0.58-0.84)
NAC when IOCM are used	7	1.12 (0.74-1.69)

CIN - Contrast-induced nephropathy
IA - Intra-arterial
IOCM - Iso-osmolar contrast media
IV - Intravenous
LOCM - Low-osmolar contrast media
NAC - N-acetylcysteine
RR - Risk ratio



AKI : PART II

Diagnosis of AKI

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History & examination :

History :

- GI loss : Vomiting, diarrhoea, haemorrhage.
- Decreased intake.
- Heart failure, hypotension.
- Procedures (Surgery, angioplasty).
- Systemic conditions (DM, HTN, IHD, PAD, jaundice).
- Infection.
- Blood in urine.
- Exposure drugs :
  i. Antibiotic exposure.
  ii. Immunosuppressive therapy (Transplant, malignancy).
  iii. Radiocontrast agent.
  iv. Herbal medicine, recreational drugs.
  v. Flank pain, anuria, hematuria.

Examination :

- Fluid status : Mucous membrane, skin turgor, sunken eyes, orthostatic hypotension.
- CNS : Stroke, neuropathy (Vasculitis).
- Heart : S3, gallop, arrhythmias, murmur, raised JVP.
- Abdomen : Compartment syndrome, bruit mass, distended bladder, palpable tender kidney.
- Extremities : Peripheral pulses (PAD), rash (Vasculitis).
- Rectal and pelvic examination.

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Diagnostic work-up for AKI in ICU :

AKI

Baseline Investigations

- full blood count with differential
- urine dipstick
- urine microscopy (if available)
- renal ultrasound
- serum calcium

If cause of AKI remains unclear AND hypovolaemia and obstruction excluded
OR any of the above investigations abnormal:
consider the following investigations depending on clinical context and presentation

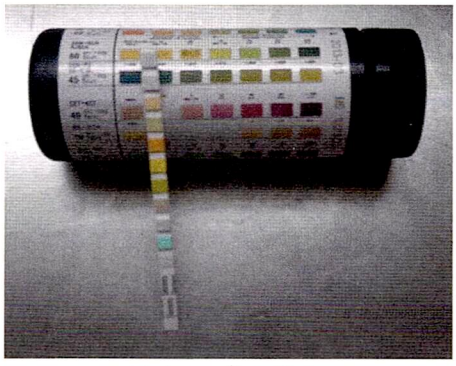
Suspected Aetiology of AK	Specific investigations to consider
Glomerulone-phritis / Vasculits	ANCA ANA Anti-GBM Anti-ds-DNA C3 / C4 ENA immunoglobulins cryoglobulins hepatitis serology HIV serology renal biopsy
Interstitial nephritis	serum eosino-phils eosinophiluria renal biopsy
Abdominal compartment syndrome	intravesicular pressure
TTP / HUS	fragmentocytes LDH platelets reticulocytes haptoglobin bilirubin
Rhabdo-myolysis	CK myoglobin
Myeloma	serum/ urine protein-electropho-resis renal biopsy
Sepsis	sepsis screen
Drug nephro-toxicity	drug levels serum eosinophils
Cardio-renal syndrome	troponin CK-MB NT-proBNP cardiac imaging

Urine analysis :

- Reagent/dipstick analysis.
- Microscopic analysis.

Dipstick analysis :

- Qualitative & easy to interpret.
- Quick bedside assessment.
- Eosinophils : Acute interstitial nephritis.
- Leukocytes/pus cells : Pyelonephritis.



Urine dipstick

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pH	• Normal range : 4.0 to 7.8 • Acidic : UTI • Alkaline : Infection with urea splitting organisms, diuretic therapy, nasogastric suction.
Hemoglobin	• RBC & Hb : Glomerulonephritis. • Hb : Intravascular hemolysis or rhabdomyolysis.
Protein	• Detect only albumin. • Physioloical : 150 mg/d. • Microalbuminuria : 30–300 mg/d (Not detected). • Nephrotic range : >3 g/d (Glomerulonephritis). • Tubular range : 1–2 g/d (Acute tubular necrosis). • Gammopathies : Globulin (Not detected).
Osmolality	• Normal : 500–800 mOsm/kg. • Increased : SIADH, pre renal AKI. • Decreased : DI, polydipsia, renal AKI.
Specific gravity	• Normal : 1.003 to 1.030 • Increased : Pre renal AKI, glycosuria, SIADH. • Decreased : Renal AKI, DI, ATN, GN.
Glucose	• Renal threshold : 160–180 mg/dl.
Ketones	• Diabetic & starvation ketosis. • False positive : Sulphhydryl groups, e.g. Captopril.
Leukocyte esterase	• Dipstick is sensitive for leucocytes even after lysis. • UTI
Nitrites	• Bacteria convert nitrates to nitrites. • False negatives : Alkaline urine.

Microscopic examination :

- Red blood cells (RBCs).
- White blood cells (WBCs).
- Epithelial cells.
- Bacteria, yeast and parasites.
- Trichomonas.
- Crystals.
- Electrolytes.
- Casts & sediments.

Electrolytes :

- Spot urine Na :
  - Urine Na <10 mmol/L = Pre-renal.
  - Urine Na >40 mmol/L = Renal.
- Fractional excretion of Na (FeNa) = $\frac{\text{Urine Na} \times \text{Plasma creatinine}}{\text{Plasma sodium} \times \text{Urine creatinine}}$
  - FeNa <0.01 (<1%) : Pre-renal.
  - FeNa >0.02 (2%) : Renal or post-renal.
  - FeNa 1–2% : Indeterminate significance.

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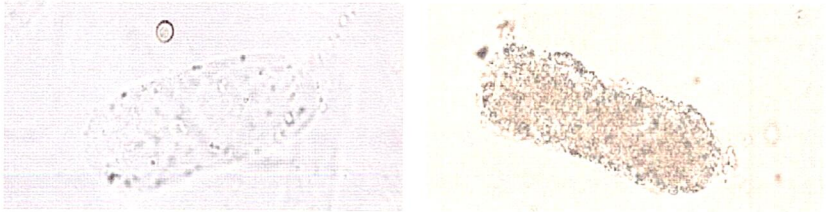
- Problem with urine electrolytes : Single measurement won't give an accurate assessment & values can be affected by diuretics, Aminoglycosides, cardiopulmonary bypass etc.

Sediments/casts :

- Elongated cylindrical formed element.
- Originate in the distal tubules or collecting ducts from a matrix of Tamm-Horsfall protein.

Hyaline casts	• Tamm-Horsfall protein. • Non pathological.
Granular casts	• Sloughed tubular cells form a dark, granular cast, muddy brown cast of acute tubular necrosis.
Cellular casts	• RBC casts : a. Normal = upto 5 RBCs. b. Dysmorphic RBC : Glomerular in origin. c. Abnormal numbers of RBC may be present in : i. Glomerulonephritis. ii. Renal thrombosis. iii. Ureteric colic. iv. UTI. • WBC casts : a. Normal = 1–3 WBC HPF. b. Leukocytes in the urine are polymorphonuclear neutrophils. c. Seen in pyelonephritis, interstitial nephritis & glomerulonephritis. • Eosinophiluria : a. Allergic interstitial nephritis. b. UTI. c. Atheroembolic renal failure.
Lipids	• Nephrotic syndrome. • Heavy proteinuria.
Waxy cast	• Broad granular cast. • CKD.
Fatty cast	• Nephrotic syndrome.



Sediments in urine

Imaging :

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Imaging modality	Salient points
Renal USG	• Normal anatomy : Length = 10–12 cm, cortical thickness >3cm. • Abnormal : Length <9cm & cortical thickness <2cm. • CKD : Small, shrunken kidney, loss of CMD (Cortico-medullary differentiation). • ↑ Kidney size : Infiltrative diseases (Amyloidosis), renal vein thrombosis. • Stone, tumor, cyst, dilated pelvicalyceal system can be visualized.
Doppler based resistive index (RI)	• Pulsed wave doppler mode. • Measured in the interlobar arteries. • RI = (Peak systolic velocity-end diastolic velocity)/peak velocity. • RI is normal if <0.70 • Indicator of renal vascular resistance & blood flow.
CT	• Ureteral stone, retroperitoneal fibrosis. • Extra renal cause of obstruction.
MRI	• Detailed assessment of renal anatomy, tumours & infections. • MRI does not play a role in routine diagnostic workup of AKI.

Renal biopsy :

- Indicated in :
  - Diagnosed AKI clinically.
  - Normal size kidney.
  - Do not recover clinically after 4 weeks.
- Urine analysis, microscopy, lab investigation suggest intrinsic renal cause.
- Pre renal and post renal causes have been ruled out.

Biomarkers in AKI :

- Noninvasive and inexpensive.
- Easily detectable in accessible samples like serum or urine.
- Highly sensitive & specific for AKI, also in the presence of concomitant injury involving other organs.
- Rapidly and reliably measurable.
- Capable of early detection of AKI.
- Able to give insight into aetiology, nature, and duration of insult.
- A marker of injury in addition to marker of function.
- Predictor of AKI severity and reversibility.
- Helpful in monitoring course and the response to interventions.
- Useful as surrogate end point for clinical interventional studies.
- Unaffected by other biological variables.

----- Active space -----

Cystatin C	• Synthesized & released into plasma by all nucleated cells at a constant rate. • Small size & positive charge at physiologic pH makes it freely filtered at the glomerulus. • Renal tubular cells take up cystatin C & can't be measured in urine. • Plasma cystatin C is used to estimate GFR. • Urine cystatin C is a biomarker of tubular cell integrity. • Confounders : Steroids, thyroid dysfunction. • Plasma cystatin C can predict development of AKI, requirement for RRT & superiority over serum creatinine.
NGAL	• 25-KDa protein, covalently bound to gelatinase of neutrophils. • Expressed at low concentration in various human tissues including kidney, trachea, lungs, stomach & colon. • Expression ↑ greatly in presence of inflammation & injured epithelia including renal damage. • Diagnostic accuracy of plasma/serum NGAL was similar to that of urine NGAL. • Validated in multiple patient populations. • Available as bedside test. • Upregulation of intrarenal NGAL can be detected in the urine as early as 2 hours after ischemic or nephrotoxic kidney injury. • Plasma NGAL is closely linked to infection & inflammation. • Urinary NGAL results predominantly from tubular production & secretion. • The thick ascending limb & the collecting duct are the predominant sites of intrarenal NGAL production. • Plasma NGAL is freely filtered by the glomerulus & taken up by the proximal tubular cells, but impaired tubular reabsorption may result in further increases of its urinary concentration.
KIM-1	• 38.7-KDa type I transmembrane glycoprotein, normally not found in urine. • ↑ Expression in presence of ischemic & nephrotoxic renal injury. • KIM-1 plays a role in renal injury and repair. • Role in prediction of early AKI is variable, depends on time of measurement.
TIMP2 IGFBP7	• Studies were done associated with cardio-thoracic surgeries. • Involved in G_1 cell cycle arrest during very early phases of cellular injury. • Markers of tubular stress. • Product of TIMP-2 x IGFBP-7 • Strong predictor of development of KDIGO stage 2/3 AKI. • >0.3 = risk of AKI, >2 = very high risk of AKI. • High specificity

(NGAL = Neutrophil gelatinase associated lipocalin, KIM-1 = Kidney injury molecule-1, TIMP2 = Tissue inhibitor metalloproteinase-2, IGFBP7 = Insulin like growth factor binding protein-7).