Acute Kidney Injury

Revise Nephrology 2021

Dr. Surjit Taraftdar
Nephrologist and General Physician
Blacktown Hospital, Sydney

Conjoint Senior Lecturer
Department of Medicine, Western Sydney University
When do I call it ‘Acute Kidney Injury (AKI)’

- **AKI** evolved from the term ARF to reflect that small decrements in renal function though not causing overt FAILURE lead to adverse outcome if not detected and treated
- Definition is based on either
  - An increase in serum creatinine above baseline levels or
  - A fall in urine output

**AKI definition as per KDIGO guidelines**
- Increase in SCr by > 0.3 mg/dl (26.5µmol/l) **within 48 hours or >50% in 7 days**
- Urine volume < 0.5 ml/kg/h for 6 hours

**AKIN guidelines**
- Increase in serum creatinine of ≥0.3 mg/dL (26.5µmol/l) or ≥50% **within 48 hours**
- Urine output of <0.5 mL/kg/hour for >6 hours
### ‘AKIN’ staging of severity

<table>
<thead>
<tr>
<th>Stage</th>
<th>Creatinine* change over baseline</th>
<th>Oliguria criteria*</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Increase in serum creatinine of ≥0.3 mg/dL (≥27µM) or within 48 hours or to 150 to 200% baseline</td>
<td>&lt;0.5mL/kg/hr for &gt;6 hours</td>
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<td>2</td>
<td>Increase in serum creatinine of 200 to 300% above baseline</td>
<td>&lt;0.5mL/kg/hr for &gt;12 hours</td>
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<td>3</td>
<td>Increase in serum creatinine to &gt;300% baseline OR Increase in serum creatinine to ≥4.0 mg/dL (≥354 µmol/L) OR initiation of RRT</td>
<td>&lt;0.3mL/kg/hr for 24 hours or anuria for 12 hours</td>
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- **KDIGO diagnosis and stage 1:** Increase in serum creatinine of ≥0.3 mg/dL within 48 hours or ≥50% within 7 day (rest similar between AKIN and KDIGO)
Importance of AKI

- High attendant morbidity and mortality - 50% in-hospital mortality if dialysis required (increases with failure of other organ systems)
- Associated with increased CKD risk in survivors
- Pre-renal and post-renal forms are rapidly reversible with treatment
- Diagnosis of ‘renal’ causes often delayed
Increasing incidence of AKI

- In USA between 2000 and 2014, AKI-related hospitalizations increased by 140% in diabetic and 230% in nondiabetic individuals.
- Possible factors contributing to the rise in the incidence of AKI:
  - Aging population
  - Rising incidence of comorbidities that affect susceptibility to AKI e.g., DM, HTN, CCF, CKD and cancer
  - Increasing clinician awareness about AKI
  - Use of more sensitive definitions for the diagnosis of AKI (leading to inclusion of less severe AKI)
  - Increased use of nephrotoxins such as newer chemo agents
  - Increasing frequency of invasive and surgical procedures

Prognosis of AKI in the elderly

- Data from US Renal Data System (USRDS):
  - Patients aged 67 years or older who developed AKI were 6.7 times more likely to develop ESRD by two years after discharge compared with those without renal injury
  - Patients with a history of CKD who developed AKI had a 41-fold increase in the risk of ESRD

‘Acute kidney injury increases risk of ESRD among elderly’
Aulshani A, Xue JL, Himmelfarb J, Eggers PW, Kimmel PL, Molitoris BA, Collins AJ
Causes of AKI

Pre-renal causes (commonest in community-up to 70%)

- **True volume depletion** - gastrointestinal loss (vomiting, diarrhoea, bleeding); renal losses (diuretics, glucose osmotic diuresis); skin or respiratory losses (insensible losses, sweat, burns); third space sequestration (crush injury)

- **Hypotension** - Decreased BP from shock (hypovolemic, myocardial, or septic)

- **Drugs** - Cause pre glomerular vaso-constriction i.e. NSAIDs, Calcineurin inhibitors (cyclosporine, tacrolimus) OR post glomerular dilatation i.e. ACE-inhibitors or angiotensin II blockers OR cause volume depletion i.e. diuretics

- **Oedematous states** - decreased cardiac output in CCF and splanchnic venous pooling and systemic vasodilation in cirrhosis causing reduced renal perfusion (Hepatorenal syndrome)
Causes of AKI

Renal causes of AKI (intrinsic renal pathology)

- **Glomerular**: Glomerulonephritis, thrombotic microangiopathy, vasculitis
- **Tubulo-interstitial**: The commoner acute tubular necrosis (ATN) and acute interstitial nephritis (AIN)

ATN defined by histologic changes—necrosis of the tubular epithelium and occlusion of the tubular lumen by casts and cell debris; 3 major causes of ATN are:

- **Renal ischemia** — All causes of severe prerenal AKI particularly hypotension, shock and surgery
- **Sepsis**— Usually associated with hypotension
- **Nephrotoxins**— aminoglycosides, vancomycin, cisplatin, radiocontrast material, cidofovir
Tubulointerstitial causes of AKI continued.....

Acute interstitial nephritis (AIN)

- Drugs (NSAIDs, penicillins, cephalosporins, ciprofloxacin, PPIs, diuretics etc.): 70 to 75%
- Infections: 4-10%
- Tubulointerstitial nephritis and uveitis (TINU) syndrome: 5-10%
- Sarcoidosis, Sjögren’s syndrome, SLE and others: 10-20%
Post renal cause of AKI

- Any cause of obstruction to urine flow downstream of kidneys:
  - Ureteric obstruction (bilateral), bladder neck or urethral obstruction e.g. stone, clot, enlarged prostate
  - Ureteric obstruction to a single functioning kidney
Causes of AKI in hospitalised patients

- ATN - 45 percent
- Prerenal disease - 21 percent
- Acute superimposed on CKD - 13 percent (due to ATN or prerenal disease)
- Urinary tract obstruction - 10 percent (most often older men with prostatic disease)
- Glomerulonephritis or vasculitis - 4 percent
- AIN - 2 percent
- Atheroemboli - 1 percent
- Prerenal causes lead to 70% of community AKI
Evaluation of the patient with AKI

- **History**: A good history or checking hospital notes often very helpful e.g. diarrhoea/vomiting/recent radiocontrast exposure/starting or increased dose of diuretics/urinary stones/NSAIDs/herbal medicines etc.

- **Physical examination**: volume status as hypovolemia suggests pre-renal cause while euvolemia suggests renal or post renal cause
  - Palpable bladder: indicates obstructive uropathy from bladder neck pathology
  - Skin rash: may indicate renal vasculitis, or allergic interstitial nephritis

- **URINE DIPSTICK**: should be considered part of initial renal evaluation as haematuria/proteinuria may suggest renal cause of AKI i.e. GN
Evaluation of the patient with AKI

- Rule out obstruction with USG
- EUC - for diagnosis/monitoring progress; high K requires urgent medical therapy and/or dialysis
- GFR not useful as creatinine changes rapidly both during AKI and recovery
- Serum Cystatin C and Urinary NGAL (U NGAL) may be helpful in diagnosing AKI in the first 48hrs of renal injury as both are detectable in this early phase
- FBC - disproportionate anaemia may indicate underlying myeloma or microangiopathic haemolytic anaemia e.g. HUS or TTP
- Myeloma screen
- LFT - if abnormal may indicate possibility of Hepato-renal syndrome (HRS)
- Coagulation - If abnormal may indicate sepsis or HRS. A normal coagulation profile is pre-requisite for renal biopsy or central line insertion for dialysis
- Blood gas - For assessing acid base status which may indicate need for dialysis
- Renal biopsy when renal cause suspected e.g. GN, nephrotic syndrome, TTP, HUS etc.
Evaluation of the patient with AKI

- **Urine dipstick**: Extremely valuable bedside investigation; haematuria and/or proteinuria (and no suspicion of urinary infection) points towards intrinsic renal cause of AKI like glomerulonephritis or renal vasculitis.

- Send urine for dysmorphic red blood cells and RBC casts if haematuria seen (with no evidence of UTI, stones or anatomical lesions on USG).

- White cell cast may indicate AIN.

- 4+ proteinuria with hypoalbuminemia and oedema points towards nephrotic syndrome (though nephrotic syndrome usually does not present with AKI).
AKI evaluation; role of Urinary Na

- **Urine sodium concentration**: low in prerenal AKI (less than 20 mEq/L) in an attempt to conserve Na and high in ATN (more than 40 to 50 mEq/L) due to impaired tubular function induced by the tubular injury.

- **Fractional excretion of sodium**: Better indicator than above

\[
\text{FENa, percent} = \frac{\text{UNa} \times \text{SCr}}{\text{SNa} \times \text{UCr}} \times 100
\]

FENa < 1% usually indicates prerenal AKI (indicative of sodium retention) and above 2% indicates ATN (damaged tubules unable to reabsorb Na).

**NOTE** - Some exceptions e.g. <1% in ATN associated with cirrhosis or CCF and >2% in those on diuretics OR in prerenal AKI due to volume expansion from excessive fluid replacement.
Coarse Granular glomerular deposits

- Low Complements
  - Infectious GN
    - Lupus GN
    - Endocarditis
  - Cryoglobulinemia
  - Membrano-proliferative/mesangiocapillary GN (MPGN/MCGN)

- Normal Complements
  - Pauci-immune glomeruli (no findings on IF)
    - ANCA positive Vasculitis
      - Granulomatosis with polyangitis (PR3 ANCA positive)
        - Microscopic polyangitis (MPO ANCA Positive)
  - Linear glomerular deposits
    - Anti-GBM antibody positive
      - Goodpasture disease
Presence of dysmorphic RBCs or RBC cast in urine - suspected GN

- Serum complements (low in post-infectious nephritis, lupus nephritis, nephritis associated with endocarditis and cryoglobulinemia)

- Blood cultures and antistreptococcal antibodies in case of suspicion of post infectious GN when there is history of preceding pharyngitis or impetigo

- ANA, ENA, Ds-DNA to exclude lupus nephritis

- Hepatitis and myeloma screen (to exclude cryoglobulinemic nephritis and mesangio-capillary glomerulonephritis)

- ANCA (rule out vasculitis e.g. PR3 ANCA positive granulomatosis with polyangitis and MPO ANCA positive microscopic polyangitis)

- Anti-GBM antibody to rule out Goodpasture syndrome
Treatment of AKI

- Fluid resuscitation
- Monitoring of urine output, fluid balance chart and daily weight to assess volume status
- Cease nephro-toxic and non-essential medications e.g. ACE inhibitors, ARBs, diuretics, NSAIDS, aminoglycosides and sometimes drugs that can cause interstitial nephritis e.g. antibiotics, PPIs
- Metformin is in itself not nephrotoxic but as it is renally cleared, it is held to protect against lactic acidosis given that many of these patients are acidotic
AKI management

- Dose adjustment of drugs as per changing renal function to avoid accumulation with resultant toxicity
- Urgent antibiotic treatment initiation if sepsis suspected
- Treat the underlying cause e.g. hypercalcemia in myeloma causing AKI needs aggressive hydration while cast nephropathy in myeloma causing AKI needs urgent steroids/anti-myeloma treatment

*Recovery phase of ATN:* Patient may have marked polyuria as tubular recovery lags; patient will need sufficient fluid replacement to prevent second hit of AKI from dehydration
Life threatening complications of AKI

- Hyperkalaemia
- Severe acidosis
- Hypoperfusion
- Fluid overload
- Pericarditis/pericardial effusion
Management of hyperkalaemia

- If ECG changes present then stabilise the heart
  - ECG and cardiac monitor
  - IV Calcium gluconate (e.g. 10ml 10% calcium gluconate)
  - Dose can be repeated every five minutes if necessary

- Shift potassium into cells
  - Nebulised salbutamol
  - Insulin/dextrose bolus or infusion
  - IV NAHCO3 if acidotic

- Remove potassium from the body
  - IV saline and frusemide (in the absence of severe AKI)
  - Haemodialysis
  - Patiromer, Calcium or Sodium polystyrene resin (take hours to act)
Indications for dialysis in AKI

- Complications refractory to medical treatment - where dialysis is indicated:
  - Refractory hyperkalaemia especially with ECG changes
  - Pulmonary oedema
  - Acidosis (pH < 7.15)
  - Uraemic encephalopathy
  - Uraemic pericarditis
Pharmacologic agents

- Multiple studies have ruled out role for dopamine
- Frusemide does not enhance renal recovery; neither reduces dialysis requirement or mortality
- Role for frusemide to treat fluid overload/pulmonary edema at least temporarily while buying time to arrange dialysis
- No known pharmacological therapy known to cure AKI
Radiocontrast Nephropathy (RCN)

- Usually reversible form of ATN
- >25% increase in SCr in 48 hours without another identifiable cause
- Clinically different from other causes of ATN due to the rapid improvement in renal function (typically within 3-7 days)

Risk factors:
- Pre-existing CKD or low renal perfusion (e.g., CCF, dehydration)
- Age >70
- Multiple myeloma
- Diabetes
- Volume and type of contrast media used (high osmolar contrast more nephrotoxic)
- Inpatients (independent risk factor)
- Drugs like NSAIDs, ACE inhibitors and ARBs
Pathogenesis: both renal medullary hypoxia due to vasoconstriction and direct tubular injury lead to ATN.
Unlike other types of ATN, rapid recovery.
AKI usually within 24 - 48 hours of contrast administration and improvement within three to seven days.
Treatment- avoid nephrotoxins, pre and post IV hydration with 0.9% saline or NaHCO3.
No longer recommended: oral NAC.
Use the lowest necessary total dose of low-osmolality or iso-osmolality contrast medium.

‘Contrast-Associated Acute Kidney Injury’, Roxana Mehran, M.D., George D. Dangas, M.D., Ph.D. and Steven D. Weisbord, M.D.

May 30, 2019
DOI: 10.1056/NEJMr1805256
Atheroembolic Renal Disease

- Cholesterol crystal embolization to the kidneys
- Usually after coronary angiography or angioplasty (commonest), renal angiography or cardiovascular surgery
- AKI several weeks later (sometimes within 1-2 weeks)
- Urine bland
- Cyanosis or discrete gangrenous lesions in the toes with intact peripheral pulses (blue toes), livedo reticularis, GI symptoms with pain/bleed, focal neurologic deficits, orange plaques in the retinal arterioles (Hollenhorst plaques)
- May have eosinophilia, eosinophiluria, and hypocomplementemia
- Definitive diagnosis by renal biopsy showing cleft like spaces within arteries (cholesterol ghosts)
- Supportive therapy and secondary prevention of CV disease with aggressive lipid lowering therapy
Pedal ischaemia

Dusky discolouration
Of all toes
Acute Interstitial Nephritis (AIN)

- Caused by inflammatory infiltrate in the renal interstitium (glomeruli normal)

- Associations:
  - Drugs (antibiotics, NSAIDs, diuretics and PPIs) - 70 to 75%
  - Infections (streptococcus, legionella, CMV etc.) - 4 to 10%
  - Tubulointerstitial nephritis and uveitis (TINU) syndrome - 5 to 10 %
  - Systemic disease including sarcoidosis, Sjögren's syndrome, SLE and others - 10 to 20 %
Acute Interstitial Nephritis (AIN)

- **Presentation:**
  - May present from few days to months after drug exposure
  - Rash - 15 %; Fever - 27 %; Eosinophilia - 23 %
  - Triad of rash, fever, and eosinophilia - 10 %

- **Diagnosis:**
  - History/above presentation/urine showing white cells or white cell casts and sometimes eosinophiluria indicate diagnosis
  - Renal biopsy definitive but usually not be needed

- **Treatment:**
  - Discontinuation of the potential causative agent is mainstay of therapy
  - 2-3 months course of prednisolone in those whose creatinine does not improve within 7 days of stopping offending drugs
Aminoglycosides freely filtered across glomerulus and partially taken up by the proximal tubular cells

Gentamicin levels inside PTC cells 100 to 1000 times serum levels......toxic to the cells

Non-oliguric AKI due to ATN usually occurs 5-10 days after treatment

Once daily dosing better from the nephrotoxicity perspective: higher peaks for shorter periods and prolonged period of very low exposure may allow for more efficient handling and excretion

Hypomagnesaemia, hypocalcaemia and hypokalemia may be seen due to tubular defects
Hepatorenal Syndrome

- HRS is a **reversible** and **functional** renal failure that occurs in patients with acute or chronic liver disease and **portal hypertension**

- Diagnosis of exclusion- rule out prerenal/renal//postrenal causes

- Incidence in cirrhotic patients with normal renal function is 18 and 39% at 1 and 5 years respectively

- Neither etiology of cirrhosis nor the Child Pugh score predicts HRS

- Caused by marked renal vasoconstriction causing low GFR in the face of vasodilatation of splanchnic vessels
Diagnosis

- Not pre or post renal failure/ recent nephrotoxic drugs/infections
- Serum creatinine > 133 umol/l
- No significant haematuria(<50 RBC/HPF) and none or minimal proteinuria (< 500 mg/day)
- **No improvement in renal function( to < 133umol/L) after volume expansion with intravenous albumin (1 g/kg of body weight per day up to 100 g/day) for at least two days and withdrawal of diuretics**

*Important: HRS is a diagnosis of exclusion*
Two types

- **Type 1 HRS**- Associated with doubling of serum creatinine > 2.5mg/dl (220 umol/l) or a 50% reduction in GFR to < 20ml/min in < 2 weeks. Median survival without treatment is 2 weeks.

- Often multiorgan failure and hyponatremia

- Precipitating events: bacterial infections(specially SBP), gastrointestinal bleeding, vigorous diuretic therapy, abdominal paracentesis or NSAIDs

- **Type 2 HRS**- Associated with a much less rapid decline in renal function and mainly presents with refractory ascites. Median survival without treatment is 4-6 months
Treatment (remember HRS is due to vasodilatation) with vasoconstrictors...

**Terlipressin with albumin**
- Vasopressin analogue Terlipressin (IV 1 to 2 mg/ 4 to 6 hourly) and albumin given for 2 days as IV bolus (1 g/kg per day) followed by 25 to 50 grams daily up till 15 days

**Midodrine, octreotide, and albumin where terlipressin is not available**
- Midodrine (alpha-1 adrenergic agonist) orally at 7.5 mg tds and octreotide (somatostatin analogue) at 100 mcg SC tds, increased as needed to 12.5 mg tds and 200 mcg tds respectively

**Norepinephrine with albumin for ICU patient with hypotension**
- Usually for ICU patient with hypotension

Definitive HRS treatment is liver transplantation
Heme Pigment Nephropathy (in rhabdomyolysis and hemolysis)

- Myoglobin and haemoglobin are filtered by the glomerulus into the urinary space and degraded releasing heme
- Dipstick-positive haematuria in the absence of any RBC by microscopy may be the first clue along with pigmented granular casts
- Heme can lead to AKI by three processes:
  - Tubular obstruction, possibly in association with uric acid
  - Direct proximal tubular cell injury
  - Vasoconstriction leading to medullary hypoxia
- Also in rhabdomyolysis sequestration of large amounts of fluid in the injured muscle can cause hypovolemia and pre renal AKI
- **Treatment** consists of fluid replacement and at times alkaline diuresis with intravenous bicarbonate to reduce chances of tubular obstruction
Thank you

I don't care what day it is.
Four hours is four hours.