Acute Kidney Injury

Revise Nephrology 2023

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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

Stage	Creatinine* change over baseline	Oliguria criteria*
1	Increase in serum creatinine of ≥0.3 mg/dL (27uM) or within 48 hours or to 150 to 200% baseline	<0.5mL/kg/hr for >6 hours
2	Increase in serum creatinine of 200 to 300% above baseline	<0.5mL/kg/hr for >12 hours
3	Increase in serum creatinine to >300% baseline OR Increase in serum creatinine to ≥4.0 mg/dL (354 µmol/L) OR initiation of RRT	<0.3mL/kg/hr for 24 hours or anuria for 12 hours

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 procedure

Trends in Hospitalizations for Acute Kidney Injury - United States, 2000-2014; Pavkov ME, Harding JL, Burrows NR ;MMWR Morb Mortal Wkly Rep. 2018;67(10):289. Epub 2018 Mar 16

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' Auishani A, Xue JL, Himmelfarb J, Eggers PW, Kimmel PL, Molitoris BA, Collins AJ J Am Soc Nephrol. 2009;20(1):223. Epub 2008 Nov 19

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
- **Remember: 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/ACEI or ARBS/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

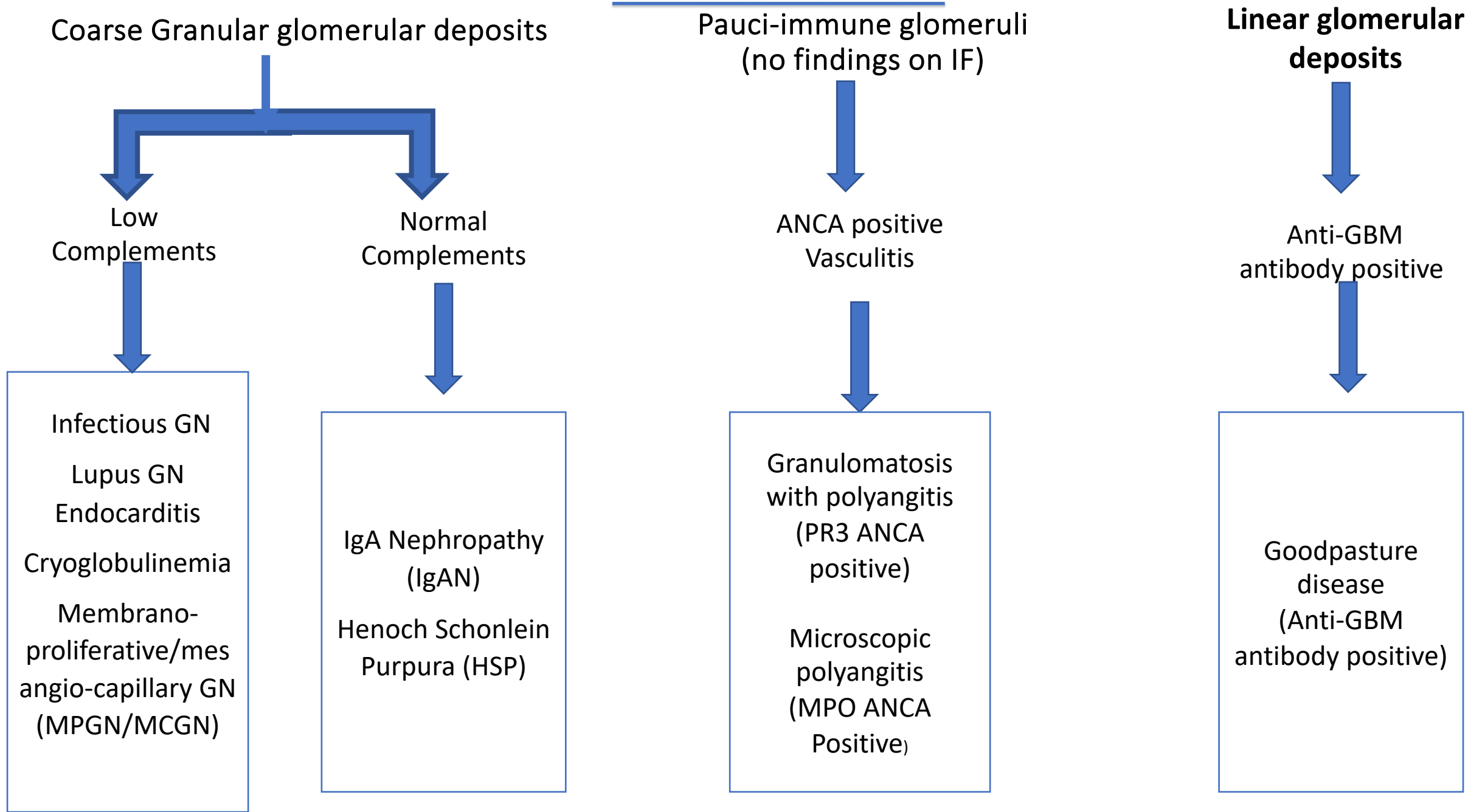
- Only use if in doubt about pre renal AKI VS ATN
- **Urine sodium concentration: low** in prerenal AKI (less than 20 mEq/L) in an attempt to conserve Na and high in ATN (more than 40 to 50 mEq/L) due to impaired tubular function induced by the tubular injury
- **Fractional excretion of sodium: Better 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- many 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

GN CLASSIFICATION



Presence of dysmorphic RBCs or RBC cast in urine- 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 (DO NOT NEED CATHETERISATION ROUTINELY)
- 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 like omeprazole
- 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(inn 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*

RCN continue…

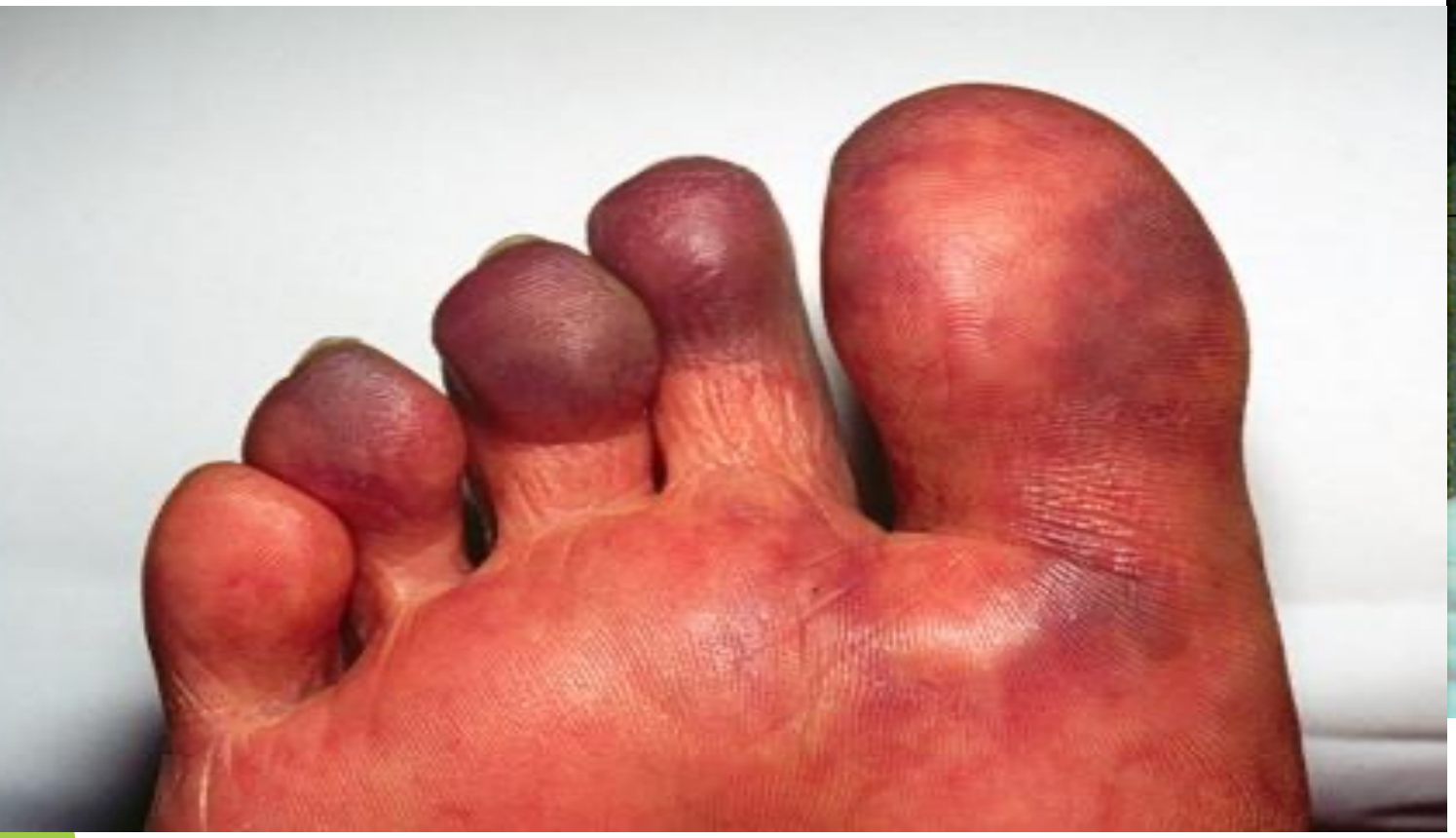
- Pathogenesis: both renal medullary hypoxia due to vasoconstriction and direct tubular injury lead to ATN
- Unlike other types of ATN, rapid recovery
- AKI usually within 24 - 48 hours of contrast administration and improvement within three to seven days
- Treatment- avoid nephrotoxins and metformin, pre and post IV hydration with 0.9% saline or $NaHCO_3$
- No longer recommended: oral NAC
- Use the lowest necessary total dose of low-osmolality or iso-osmolality contrast medium

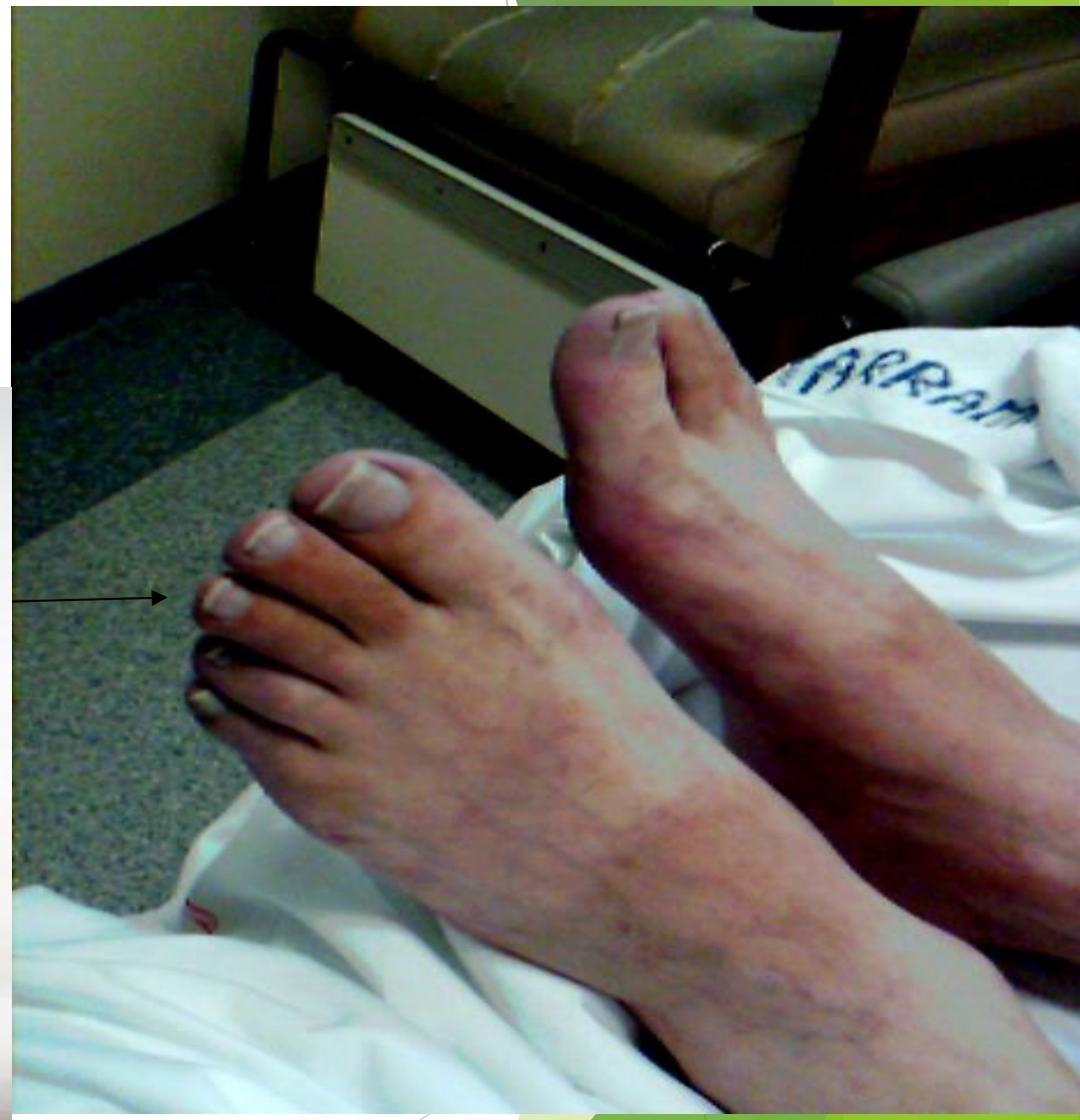
Contrast-Associated Acute Kidney Injury', Roxana Mehran, M.D., George D. Dangas, M.D., Ph.D. and Steven D. Weisbord, M.D.May 30, 2019 N Engl J Med 2019; 380:2146-2155
DOI: 10.1056/NEJMra1805256

Atheroembolic Renal Disease

- Cholesterol crystal embolization to the kidneys
- Usually after coronary angiography or angioplasty (commonest) , renal angiography or cardiovascular surgery, thrombolytic therapy, or anticoagulation
- Spontaneous event, induced by hemodynamic stress
- 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 during the acute phase
- 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





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, TB, 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)

- Onset of drug-induced AIN following drug exposure may range from 3-5 days to weeks, to many months.

- May present from few days to months after drug exposure

- Rash – 15 %; Fever – 27 %; Eosinophilia – 23 % (the full triad seen in 105 only)

-**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**

- (NSAID)-induced AIN does not generally respond to glucocorticoid therapy

Gentamicin

- 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, hypophosphatmia and hypokalemia may be seen due to tubular defects

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

My kidneys are so good at filtering, they should work at a coffee shop

Thank you