2. RENAL IMPAIRMENT

Primary Author: Jeremy Nel

Background

Patients with AHD commonly have abnormal creatinine levels. This chapter presents a useful approach to a patient with apparent renal impairment, beginning with asking if renal impairment is definitely present and whether it might be acute or chronic. It then gives an approach to dealing with both acute and chronic renal impairment.

Is the patient truly in renal failure?

Serum creatinine should not be used as the sole indicator of renal failure. One reason is that independently of renal function, creatinine also varies as a function of muscle bulk. Men, younger adults, and muscular men have a higher serum creatinine than women, older adults and wasted people, on average.

Rather than using creatinine therefore, it is far better to estimate the **glomerular filtration rate (GFR),** which considers many of the above factors. Commonly used calculations for this include:

- **Cockroft-Gault formula:** this uses sex, age, weight, and creatinine. It is relatively easy to calculate, and because weight is factored in, it's often more accurate for wasted patients such as might be seen with AHD. Technically, it measures creatinine clearance, not eGFR.
- **CKD-EPI:** this uses sex, race, age, and creatinine. It is often calculated automatically on lab reports. It is more accurate than Cockroft-Gault, apart from patients who are extremely wasted.

Both calculations are accessible on most medical Apps available on a smartphone.

Note: these equations are only meant to be used in chronic kidney disease, not acute kidney injury. In acute kidney injury, the glomerular filtration rates estimated by the above equations can be highly inaccurate. *In acute renal failure, look at the creatinine trend* too. A rapidly rising creatinine implies that the GFR is worse than the equations calculate. A falling creatinine implies that the GFR is better than the equations calculate.

Note: some medications inhibit creatinine's secretion directly, without affecting renal function. Dolutegravir is one such medication. Because the above equations use creatinine to estimate the GFR, a patient who is started on dolutegravir can expect their serum creatinine to rise and their eGFR to appears to fall, but *this does not reflect a true decline in renal function.* In the case of dolutegravir, the estimated rise in creatinine is usually <25%, and it occurs within the first few weeks after initiating the medication. A rise of >20-25% in serum creatinine, or a rise that occurs after the first month, should prompt workup for alternative causes (the median rise in creatinine seen in the ADVANCE trial was almost 20%).

Is the renal dysfunction likely acute or chronic?

This is a hard question to answer, but it has important implications. In acute kidney injury (AKI), urgent intervention is required for the kidney function to recover, whereas in chronic kidney disease (CKD), management is less urgent and often centers around risk factor modification to prevent gradual worsening, rather than on renal recovery.

Clues that suggest acute vs chronic kidney injury are shown in table 1.

TABLE 1: Clinical clues to differentiate acute kidney injury (AKI) from chronic kidney disease (CKD)

Clue	This suggests	Comment
Small kidneys (< 9 cm) on ultrasound/CT scan	CKD	Note that some causes of CKD have normal/large kidneys (e.g. HIVAN, diabetic nephropathy, etc.)
A previous normal creatinine within the last 3 months	AKI	Chronic kidney disease is defined as renal dysfunction lasting at least 3 months.
Normal haemoglobin	AKI	99% of CKD patients have anaemia. Many patients with AKI also have anaemia from other causes, so anaemia itself isn't helpful – but the absence of anaemia is and would be suggest that it is not CKD
High serum phosphate	CKD	Not that phosphate levels can change quickly (within days)
Oliguria	AKI	Note that end-stage CKD patients will also be oliguric, and some AKI patients can be polyuric.

The clinical context is also important to distinguish between AKI and CKD. A patient with AKI is usually acutely ill in some obvious way (e.g. diarrhoea, pneumonia, dehydration, septicaemia).

However, a patient with CKD can develop a superimposed AKI ("acute-on-chronic renal dysfunction"). In that case the acute and chronic components will need separate management, as outlined below. If in doubt, treat as if it is AKI first, but be careful to watch for signs of fluid overload.

Acute renal failure (acute kidney injury – AKI)

Common causes of AKI are:

- **Pre-renal AKI** – hypoperfusion of the kidney, often from dehydration or sepsis. This will respond to fluids. If renal perfusion is not rectified, progress to acute tubular necrosis occurs (see below).
- **Acute tubular necrosis (ATN)** – from either ischaemia because of hypoperfusion, or from toxins (usually medications). Important medications that cause ATN include:
  - Nonsteroidal anti-inflammatory drugs (NSAIDs)
  - Aminoglycosides
  - Amphotericin B
  - Tenofovir (rarely)
- **Acute interstitial nephritis** – this is inflammation of the interstitium with or without renal tubular injury. Urine eosinophils are virtually pathognomonic but are only present in the minority of cases. Important medications that can cause acute interstitial nephritis include:
  - Rifampicin
  - Cotrimoxazole (Bactrim)
  - NSAIDs
  - Herbal remedies

Management principles

Below is a list of management principles in acute kidney injury (AKI):

- Give a trial of fluids if there is a suspicion of a pre-renal component to the AKI (unless the patient is clinically overloaded). Most septic or dehydrated patients will respond at least partially to fluids. E.g., give 1 litre of an isotonic crystalloid like normal saline over 30 minutes, then 3 litres per day thereafter. Assess the patient carefully for signs of fluid overload before each litre. If signs are present, stop giving fluids.
- Stop all commonly nephrotoxic medications, like NSAIDs, tenofovir, and cotrimoxazole.
- Dose-adjust any other medications that trequire dose adjustment if there is renal compromise, like pyrazinamide and ethambutol.
- Attempt to correct any metabolic derangements. Pay particular attention to hyperkalaemia.
- Treat the underlying cause (e.g., diarrhoea, pneumonia).
- If there is reason to suspect urinary obstruction (e.g., a history of prostate enlargement, cervical cancer, or kidney stones), obtain an urgent ultrasound to exclude this possibility.
- Assess for the need for acute dialysis. Indications for dialysis include:
  - Acidosis refractory to medical therapy
  - Hyperkalaemia refractory to medical therapy
  - Refractory pulmonary oedema
  - Uraemic gastritis
  - Uraemic pericarditis
  - Uraemic encephalopathy

BOX 1: A note on tenofovir use in acute kidney injury (AKI)

- Tenofovir (TDF) should be stopped as it may be contributing to AKI, even if it's not the primary cause. However, don't stop all antiretrovirals– rather change the TDF to another antiretroviral (like abacavir).
- If there is a non-TDF cause for the AKI, TDF can be reintroduced aonce renal function normalises. If the patient has had severe renal dysfunction, it is advisable to wait at least 1-3 months after renal function normalises before reintroducing TDF.
- **Remember:** TDF is a very rare cause of AKI in the absence of a second insult to the kidneys. Therefore, never assume that all you need to do is to stop the TDF. Consider other causes as here is a very high probability that there is another issue as well.

Chronic kidney disease (CKD)

There are two main aspects to consider in CKD:

1. HIV-associated nephropathy (HIVAN)

HIVAN is a direct HIV infection of the renal cells, causing a changes in the glomerulus (collapsing variant of focal segmental glomerulosclerosis), interstitium (plasma cell infiltrate) and tubules (dilated tubules lined by flat epithelium with filled with proteinaceous material).

HIVAN can only be diagnosed definitively on renal biopsy, but a typical picture highly suggestive of HIVAN can be easily identified. This includes:

- Advanced HIV (high viral load and low CD4, though there are exceptions)
- Black race (HIVAN is strongly associated with a particular genetic variant of the APOL1 gene).
- Large or high to normal sized kidneys (typical size range is 10.5-15.5 cm)
- Nephrotic or subnephrotic ranged proteinuria
- Bland urinary sediment (no significant amount of red or white cells in the urine)
- Absence of significant oedema or hypertriglyceridaemia (which often accompanies other forms of nephrotic syndrome)

Management of HIVAN

This is in addition to the standard management of CKD (see below) and includes:

- Initiate antiretroviral therapy urgently (to prevent a rapid decline in GFR).
- Give an ACE-inhibitor if the patient is significantly proteinuric (>1g per day). The benefit of this in HIVAN is not well established and is largely extrapolated from the management of other causes of nephrotic syndrome. Following initiation, monitor the potassium and GFR for 2 weeks. A slight fall in GFR is expected with an ACE-inhibitor, but this is acceptable provided it does not exceed 20%. If it exceeds 20%, stop the ACE-inhibitor.

2. General management of chronic kidney disease (CKD)

CKD can be caused has many causes (whether HIVAN or other, e.g. diabetes, hypertension, etc.) and management includes the following, regardless of the cause:

- Control relevant risk factors to prevent worsening renal function:
  - Blood pressure < 130/80
  - HBA1c < 7.0%
  - HIV viral load undetectable
- Counsel the patient about avoiding nephrotoxic drugs (e.g. NSAIDs)
- Dose-adjust any drugs that need it.
- Refer to nephrologist if the GFR is < 30 ml/min

HIV-infected patients with CKD are candidates for chronic dialysis and renal transplant in many centres.

BOX 2: Recommended first-line regimen in chronic kidney disease (CKD)

The recommended first-line antiretroviral regimen for patients with chronic kidney disease is

lamivudine (or emtricitabine) + abacavir + dolutegravir

Lamivudine and abacavir are available as a fixed dose combination. It is no longer believed to be strictly necessary to dose adjust lamivudine in renal failure; therefore, the fixed dose combination can be safely used.

BOX 3: Chronic kidney disease (CKD) and hepatitis B

What about an HIV-infected patient with chronic hepatitis B who has chronic kidney disease?

- Although lamivudine or emtricitabine have anti-hepatitis B activity, hepatitis B develops resistance to these medications after a period of time (approximately 50% resistance at 1 year, and 90% resistance at 5 years). Therefore, these medications cannot be relied on for chronic control of hepatitis B.
- Dedicated anti-hepatitis B medication, such as entecavir, are available in South Africa and can be used but they are very expensive and not routinely available in the public sector.
- Tenofovir is therefore required for control of chronic hepatitis B in most patients, even those with chronic kidney disease. Tenofovir alafenamide fumarate (TAF) may be a better option in patients with chronic kidney disease in this scenario, if it is available. The dose of tenofovir (either TDF or TAF) should be adjusted according to eGFR (see table below), and an effective antiretroviral regimen constructed around this for their HIV (this is the case even if the patient's HIV is resistant to TDF; in which case the patient may sometimes require TDF and 3 other antiretroviral drugs). In patients with CKD in whom tenofovir is added, close attention should be paid to the creatinine clearance, which should be checked at 3 and 6 months after TDF initiation at a minimum, and thereafter 6 monthly.

TABLE 2: Medication dosage adjustments in renal failure				
ART drug dosage adjustments in renal failure [Sourced from: SA HIV Clinicians Society 2017 Adult ART Guidelines]				
Drug	CrCl (mL/min)[‡§]		Haemodialysis (dose after dialysis)	Peritoneal dialysis
	10 – 50	< 10		
TDF	300 mg 48-hourly (GFR 30-50) or 72-96 hourly (GFR 10-29)	300 mg once weekly	TDF	300 mg 48-hourly (GFR 30-50) or 72-96 hourly (GFR 10-29) Unknown
TAF	25mg daily	Unknown	Unchanged	Unchanged
ABC	Unchanged	Unchanged	Unchanged	Unchanged
3TC	150 mg daily	50 mg daily	50 mg first dose and thereafter 25 mg daily[†]	50 mg first dose and thereafter 25 mg daily[†]
AZT	Unchanged	300 mg daily	300 mg daily	300 mg daily
d4T	15 mg 12-hourly	15 mg daily	15 mg daily	Unknown
NNRTIs	Unchanged	Unchanged	Unchanged	Unchanged
PIs	Unchanged	Unchanged	Unchanged	Unchanged
InSTIs	Unchanged	Unchanged	Unchanged	Unchanged

†It is no longer believed to be strictly necessary to dose adjust lamivudine in renal failure, and thus if it is more convenient (e.g. a fixed dose combination is available), the full dose may be given.

Recommended references

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