Guidelines for Medicines Optimisation in Patients with Acute Kidney Injury

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Think Kidneys is a national programme led by
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To the best of our knowledge, the contents of this publication are in line with National Institute for Health and Care Excellence guidance relating to the management and treatment of acute kidney injury.

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1. Introduction

Acute kidney injury (AKI) is the sudden loss of kidney function over a period of hours or days. Since the kidneys are one of the major excretory pathways for the removal of drugs from the body, this sudden loss of kidney function can have major implications for a patient's prescribed medication regime.

The term 'nephrotoxic' should be used with caution. Few medications truly have direct toxic effects on the kidneys, but several have the potential to impair renal function if used under certain circumstances, such as where the patient has a degree of chronic kidney disease in conjunction with hypovolaemia and acute illness. Under these circumstances, continued use of these medications may further exacerbate an episode of AKI.

The Think Kidneys Programme has taken the decision to avoid the use of the term nephrotoxic. In addition, many medications are cleared via the kidneys, so have the potential to accumulate during an episode of AKI. The result of this may be a further deterioration in kidney function, or there may be other adverse effects such a bone marrow or CNS toxicity. Hence it is necessary to review the use of these medications, and amend the doses appropriate to the level of the patient's renal function.

When a patient is either admitted with AKI, or develops AKI during an admission episode, a thorough review of medication is required in order to:

- Eliminate the potential cause/risk/contributory factor for AKI
- Avoid inappropriate combinations of medications in the context of AKI
- Reduce adverse events
- Ensure that doses of prescribed medication are appropriate for the patient's level of renal function
- Ensure that all medicines prescribed are clinically appropriate.

Points to note and questions to ask in the medicines management of these patients include:

- Which medications should be suspended?
- Which medications should not be suspended?
- Which medications may be used with caution?
- Are there any alternative therapeutic options?

If a medication must be used, in order to minimise harm:

- Amend doses appropriate to the patient's level of renal function
- Monitor blood levels of drugs wherever possible
- Keep course of treatment as short as possible
- Discuss treatment with pharmacist/microbiologist

Ensure appropriate information and advice is given on discharge:

- From the ICU to the ward
- From the ward to the GP (and care home if required)
- From the ward to the patient and their family/carers

2. Acute kidney injury – Medication Optimisation Pro forma

In order to optimise the prescribing of medications to a patient with AKI, the following points should be considered:

1. Is the patient receiving medication which may impair renal function?

• Contrast media • ACE Inhibitor • NSAIDs • Diuretics • Angiotensin receptor blocker

   Consider withholding these agents during an episode of AKI.

2. Medication

• Is the patient taking any other medications which could exacerbate AKI? Consider withholding them. • Is the patient prescribed any medications where the dose needs to be amended in renal impairment? • Amend medication doses appropriate to the patient's degree of renal impairment. • In house guidelines for drug use in AKI are recommended for example for. antibiotics, analgesia, contrast media, chemotherapy.

3. Educate the patient before discharge about which medications to restart and when, which medicines to avoid etc.

4. Ensure comprehensive information on which medications to restart and when, is communicated to the GP or next care setting.

Other useful reference sources to facilitate dose adjustment in AKI include:

Group of medicines	Suggested guidelines
Anti-retrovirals /HAART	National Institute of Health HIV/AIDS Treatment Guidelines
Chemotherapy	North London Cancer Network Guidelines
Mental Health	The Maudsley Prescribing Guidelines
General medications	The Renal Drug Database
General medications	Manufacturers' Summary of Product Characteristics

3. High risk medicines and actions

The following list of medications is not exhaustive. Remember to consider ALL medications including any 'usual' long term medications. Remember to check medication history thoroughly and ask about 'over the counter' preparations, herbal remedies/teas and alternative therapies. Check recreational use of drugs (cocaine, ketamine etc) as these have been implicated in rhabdomyolysis.

With reference to the table below, the three types of problem associated with the use of drugs in AKI are:-

1) effects on renal/fluid/electrolyte physiology
2) change in the side effect profile when renal function is reduced
3) direct action on the kidneys

This format is therefore adopted in the following table.

Drug	Effects on renal/fluid/electrolyte physiology	Change in the side effect profile when renal function is reduced	Direct action on the kidneys	Action in presence of AKI
Analgesics				
NSAIDs / COX II inhibitors	Altered haemodynamics within the kidney leading to underperfusion and reduced glomerular filtration		Acute interstitial nephritis (rare)	Avoid
Opioid analgesics		Accumulation of active metabolites (especially morphine, pethidine and codeine) – increased incidence of CNS side effects & respiratory depression		Avoid XL / SR preparations. Reduce dose and frequency. Use short acting preparations wherever possible. Use opiates with minimal renal excretion e.g. fentanyl, oxycodone, hydromorphone, tramadol.
Tramadol		May accumulate leading to increased sedation, mental confusion and respiratory depression		Reduce dose Avoid XL preparations
Benzodiazepines		Accumulation of drug & active metabolites leading to increased sedation & mental confusion		Reduce dose & monitor for excessive sedation
Antibiotics / Antifungals / Antivirals				
Aciclovir		Accumulation leading to mental confusion, seizures.	Crystal nephropathy.	Reduce dose Beware if patient is at risk of dehydration - Encourage patient to

				drink plenty
Aminoglycosides		Ototoxicity	Tubular cell toxicity	Avoid if possible. If use is unavoidable, reduce dose &/or increase dosing interval Monitor drug levels and renal function 2 – 3 times per week
Amphotericin IV – Fungizone®	Hypokalaemia		Tubular cell toxicity	Avoid rapid infusion Consider Ambisome® preparation
Co-trimoxazole	Hyperkalaemia		Crystal nephropathy	Reduce dose. Beware if patient is at risk of dehydration - Encourage patient to drink plenty
Fluconazole		Accumulation leading to acute mental confusion, coma, seizures		Reduce dose. Check for drug interactions that may be contributing to AKI, eg. consider withholding statins due to risk of rhabdomyolysis
Ganciclovir IV		Accumulation leading to neutropenia, anaemia and thrombocytopenia	Crystal nephropathy	Reduce dose Monitor renal function and full blood count Avoid rapid infusions
Penicillins		Accumulation leading to CNS side effects including seizures	Acute interstitial nephritis (rare) Glomerulonephritis	Reduce dose
Teicoplanin		Accumulation leading to CNS excitation, seizures, & blood dyscrasias		Reduce dose Monitor levels

Tetracycline		Accumulation leading to renal dysfunction, benign cranial hypertension, jaundice, hepatitis	Acute interstitial nephritis (rare)	Avoid
Trimethoprim	Increased risk of hyperkalaemia(especially in combination with spironolactone or ACEI/ARB). Interferes with tubular secretion of creatinine leading to a rise in serum creatinine (without a true change in GFR).	Accumulation leading to hyperkalaemia (particularly with high doses), nausea and vomiting	Acute interstitial nephritis (rare)	Avoid or reduce dose (particularly if patient is already taking an ACEI, ARB or spironolactone) Studies have shown that elderly patients prescribed trimethoprim have a 12 x greater risk of developing life-threatening hyperkalaemia if already taking spironolactone, and a 7-fold increased risk of life-threatening hyperkalaemia, and a 1.5 x increased risk of sudden death if already taking an ACEI or ARB.
Valganciclovir		Accumulation leading to neutropenia, anaemia and thrombocytopenia		Reduce dose Monitor renal function and full blood count
Vancomycin		Accumulation leading to renal toxicity, ototoxicity	Acute interstitial nephritis (rare)	Reduce dose / increase dose interval Monitor levels
Antiepileptics (including drugs used for neuropathic pain)				
Phenytoin		Risk of phenytoin toxicity if patient has low serum albumin levels	Acute interstitial nephritis (rare)	Monitor levels Correct phenytoin levels for uraemia and low serum albumin or measure salivary phenytoin (if assay available)

Pregabalin & Gabapentin		Accumulation leading to increase in CNS side effects		Reduce dose
Levetiracetam		Accumulation leading to increase in CNS side effects		Reduce dose
Antihypertensives				
Antihypertensives (including Ca-channel blockers, α-blockers, β-blockers, etc)		Hypotension. May exacerbate renal hypoperfusion. Risk of bradycardia with β-blockers.		Consider withholding / reduce dose depending on clinical signs Some patients who continue taking β-blockers during an episode of AKI have developed complete heart block and required temporary pacing.
ACEI / ARBs / Aliskiren	Hyperkalaemia		Altered haemodynamics. Can impair the kidneys' ability to maintain GFR when perfusion is compromised.	In some situations, e.g. heart failure with a decent blood pressure, continuing these agents might actually be helpful. If patient is hypertensive, consider alternative antihypertensive agents, eg, calcium channel blockers, thiazide-type diuretics, alfa-blockers, beta-blockers if appropriate
Thiazide & Loop Diuretics	Hypokalaemia, hypocalcaemia, hypomagnesaemia, hyponatraemia, hyperuricaemia (rare) Volume depletion	Tinnitus & deafness (usually with high doses and rapid IV administration),	Overdiuresis leading to hypoperfusion of the kidneys can cause or exacerbate AKI.	Loop diuretics (furosemide & bumetanide) preferred as thiazides less effective if GFR < 25ml/min. However thiazides can potentiate the effects of loop diuretics. Higher doses may be needed to achieve a diuresis in patients with

				fluid overload.
Potassium sparing Diuretics (Amiloride, spironolactone, eplerenone)	Hyperkalaemia		Hypoperfusion of the kidneys	Avoid
Hypoglycaemic agents		Accumulation leading to hypoglycaemia		Avoid long-acting preparations. Monitor blood glucose levels & Reduce dose if necessary
Metformin		Lactic acidosis. Accumulation leading to hypoglycaemia		Avoid if GFR < 30 ml/min Seek nephrologist advice if undergoing contrast procedure or at risk of AKI
Contrast Media			Direct tubular toxic effect. Incidence of CIN higher with high- & low-osmolar contrast media, and lower with iso-osmolar, non-ionic contrast media	Ensure patient is well hydrated pre-exposure to contrast, PROVIDED the patient is able to tolerate IV fluids. This is NOT recommended for patients with congestive heart failure pre-coronary angiogram. IV sodium chloride or sodium bicarbonate are most effective
Immunosuppressants (DMARDs, chemotherapy)				
Calcineurin inhibitors e.g. ciclosporin, tacrolimus	Increased risk of hyperkalaemia	Increased risk of neurotoxicity	Increased risk of nephrotoxicity	Seek advice of transplant centre regarding monitoring levels and dose adjustment
Methotrexate		Accumulation leading to e.g. excessive bone marrow	Crystal nephropathy	Avoid especially if patient at risk of hyperkalaemia

		suppression, mucositis, acute hepatic toxicity, acute interstitial pneumonitis		Monitor levels and consider folinic acid rescue Correct fluid balance
Others				
Allopurinol		Accumulation of allopurinol and its metabolites leading to agranulocytosis, aplastic anaemia, thrombocytopenia	Acute interstitial nephritis (rare)	Start at a low dose to avoid severe rash, but can then usually safely be titrated up against serum urate
5 – aminosalicylates			Tubular and glomerular damage.	Avoid
Antihistamines, Anti-psychotics, Antispasmodics		Anticholinergic side effects. Urinary retention.	Acute interstitial nephritis (rare)	Reduce dose Avoid XL preparations
Ayurvedic medicines		Some ayurvedic medicines also contain heavy metals	Cases of renal impairment have been reported	Avoid Check drug history thoroughly Patients may not consider herbal preparations / teas as medicines
Bisphosphonates IV			Can cause impaired renal function – especially when given in high doses and short duration infusions	Reduce dose and infuse at correct rate Advantages of correction of severe hypercalcaemia may outweigh risks: seek specialist advice
Colchicine		Diarrhoea / vomiting causing hypovolaemia	Exacerbates hypoperfusion if also taking a NSAID	Low doses e.g. 500mcg bd or tds are effective. Do not use NSAIDs for gout; if Colchicine causes unacceptable adverse effects, consider a short course of corticosteroids
Digoxin	1. Aggravates hyperkalaemia	May accumulate leading to		Reduce dose

		bradycardia, visual disturbances, mental confusion		Monitor potassium & drug levels
Herbal preparations		Cat's Claw has anti-inflammatory properties and has been implicated in causing AKI and hypotension with antihypertensives	The toxic effects of herbal remedies to the kidneys may be exacerbated when used with concomitant medicines which can affect kidney function. Chinese herbal medicines with aristocholic acid have been implicated in interstitial nephritis.	Some herbal medicines also interact with prescribed medicines, eg. St. John's Wort potentiates the effects of ciclosporin & tacrolimus. Check drug history thoroughly. Patients may not consider herbal preparations / teas as medicines
Lipid-lowering agents e.g. fibrates, statins	May cause AKI if rhabdomyolysis present	Possible increased risk of rhabdomyolysis		Stop if AKI due to rhabdomyolysis. Otherwise, continue therapy but monitor. Stop if patient develops unexplained / persistent muscle pain
Lithium	Hypernatraemia. AKI exacerbated in hypovolaemia and in combination with ACE inhibitors / ARB / NSAIDs	Accumulation leading to nausea, diarrhoea, blurred vision, fine resting tremor, muscular weakness and drowsiness, increasing confusion, blackouts, fasciculation and increased deep tendon reflexes, myoclonic twitches and jerks, choreoathetoid movements, urinary or faecal incontinence,	Chronic interstitial nephropathy (rare)	Avoid where possible Monitor lithium levels Seek advice for alternative Encourage patient to drink plenty. Patients on long-term lithium nearly always have a degree of diabetes insipidus, and are therefore at serious risk of developing hypernatraemia due to true dehydration when unwell without adequate water intake.

		increasing restlessness followed by stupor. Very rarely, it is associated with neuroleptic malignant syndrome.		Monitor serum sodium concentration
Nitrates / Nicorandil		Hypotension	May exacerbate hypoperfusion	Consider withholding / reduce dose depending on clinical signs
Anticoagulants				
Low molecular weight heparins		Risk of accumulation leading to increased risk of bleeding		Monitor anti-Xa levels and consider reducing dose or switching to an alternative agent as per local guidelines
Warfarin		INR may be raised due to acute rise in urea and warfarin displacement from binding sites		Monitor INR and consider reducing dose or withholding depending on indication for use
Direct Oral Anticoagulants		May accumulate leading to increased risk of bleeding.		Consider withholding, particularly agents with high renal clearance. Routine blood testing does not detect those people at high risk of bleeding

1. Conclusion

These guidelines are not exhaustive and are only intended to act as an aide memoire to the medicines optimisation of patients with AKI. For further advice, please contact a renal pharmacist or nephrologist.

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Checklist for medicines optimisation in patients with acute kidney injury (AKI)

1. **Is the patient on any of the following medications?**

   ACEI ☐

   ARB ☐

   Diuretics ☐

   NSAIDs ☐

   Metformin ☐

   Aminoglycosides ☐

Consider withholding them – discuss with the medical team

2. **Is the patient taking any other medications which could exacerbate AKI?** ☐

Consider withholding them

3. **Is the patient prescribed any medications where the dose needs to be amended in renal impairment?** ☐

Amend doses appropriate to level of renal function

4. **Monitor U&Es & re-assess renal function daily** ☐

5. **Monitor blood levels of relevant drugs e.g. Aminoglycosides** ☐

6. **Ensure the patient is counselled before discharge in regards to which medications to restart and when, and which medications to avoid** ☐

7. **Ensure comprehensive information on which medications to restart and when is communicated via the discharge summary to the GP and/or next care setting** ☐