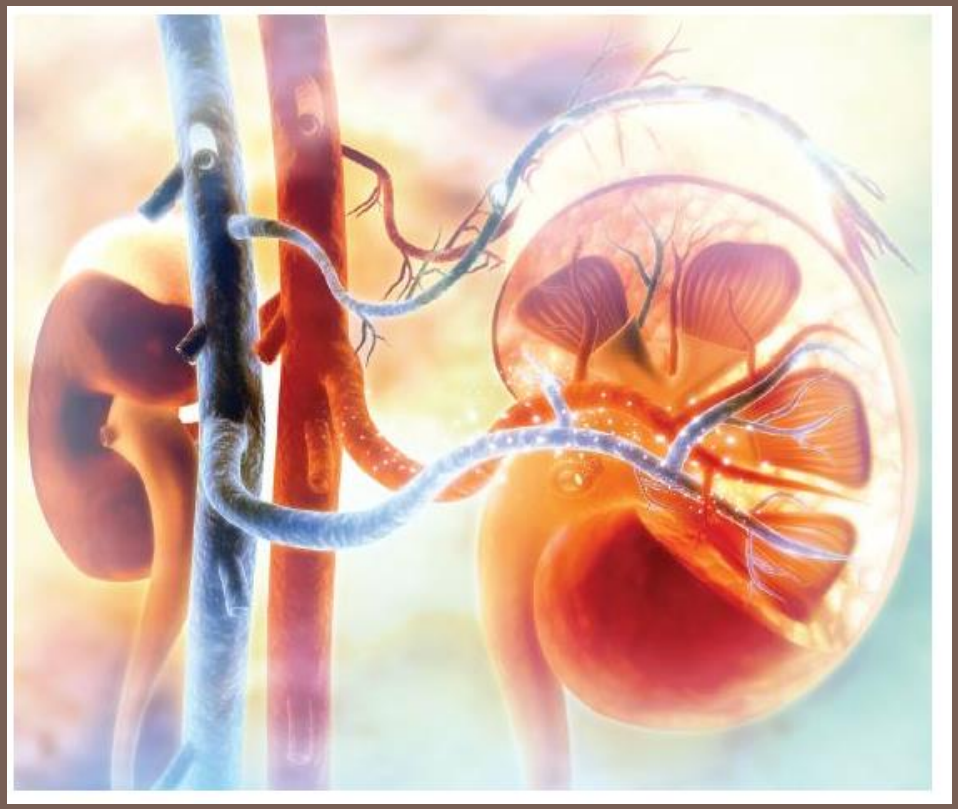


PRESCRIBING IN RENAL IMPAIRMENT

Why do we worry about renal function when prescribing?

- CKD incidence ~8%, higher in elderly patients
- Reduced renal excretion of a drug or its metabolites may cause toxicity, e.g. morphine
- Reduced efficacy/increased toxicity of some drugs is increased even if pharmacokinetics isn't affected, e.g. statins, warfarin
- Many side-effects are tolerated poorly by patients with renal impairment, e.g. NSAIDs
- Some drugs are not effective when renal function is reduced, e.g. thiazide diuretics, nitrofurantoin

Risk factors for kidney disease

- How are you going to know the patients in whom you might need to take kidney function into account?
  - Ethnicity – kidney disease more common in Asian population
  - Diabetes
  - Hypertension
  - Vascular disease (heart disease, stroke)
  - Increasing age

Pharmacokinetics (Drug handling) in renal failure

Pharmacokinetics in renal impairment

Absorption

- May be reduced due to uraemia causing nausea, vomiting, diarrhoea
- Patient may be taking phosphate binders
- May be affected by the increase in gastric pH

Distribution

- Drug-Plasma protein binding reduced – increased free (active) drug
- Uraemia increases permeability of BBB
- Volume of distribution may be altered by changes in hydration state of patient (e.g. increased Vd in oedema so need higher doses)

Metabolism

- slower in CKD leading to increased ADRs
- Vitamin D – need to use calcitriol or alfacalcidol
- Insulin – may need dose reduction

Elimination

- Glomerular filtration, renal tubular secretion and resorption all reduced
- Accumulation of drug/active metabolites highly likely
- Increased ADRs, toxicity
  - E.g. pethidine

Which of the following can we use to determine which dose of a drug to use in a patient with renal impairment?

1. Serum creatinine
2. Serum urea
3. eGFR
4. Creatinine clearance

Which of the following can we use to determine which dose of a drug to use in a patient with renal impairment?

1. Serum creatinine ✗
2. Serum urea ✗
3. eGFR ✓
4. Creatinine clearance ✓

Estimated GFR (eGFR)

- Glomerular Filtration Rate (GFR) = volume of blood filtered at the glomeruli each minute

- Labs report eGFR normalised to BSA of 1.73m^2
  - Take care if patient at extremes of body weight/BSA
    - Actual GFR = eGFR x actual BSA/1.73

- BNF advises that, for most drugs and for most adult patients of average build and height, eGFR (rather than CrCl) can be used to determine dosage adjustments. Exceptions:
  - toxic drugs
  - in elderly patients
  - in patients at extremes of muscle mass (BMI of less than 18 kg/m^2 or greater than 40kg/m^2)

  } calculation of CrCl is recommended

- Drug doses don't usually need changing until eGFR<60 (CKD stage 3-5)

Creatinine clearance (CrCl)

1. Cockcroft & Gault equation

$$\text{CrCl (ml/min)} = \frac{F \times (140 - \text{age}) \times \text{IBW}}{\text{serum Cr}}$$

F = 1.23 (male) or 1.04 (female)

IBW (men) = 50kg + (2.3kg x every inch over 5 feet)

IBW (women) = 45.5kg + (2.3kg x every inch over 5 feet)

2. Online calculators make life easier!

e.g. MDCalc

Amputations

Estimation of CrCl in patients with amputated limbs poses a dilemma for IBW calculation. A reasonable approach would be to determine the height-based IBW before the amputation, then subtract the percent of the missing limb based on data from a body segment percentage table.[18] The weight used would be the lesser of this adjusted IBW or the ABW. The average weight of body segments of a 68-kg (150-lb) man are: upper limb, 4.9%; entire lower limb 15.6%; thigh, 9.7%; leg, 4.5%; foot, 1.4%. This method for IBW calculation in amputees has not been validated for accuracy.

CrCl versus eGFR

- There is no compelling evidence to support the superiority of any given method for drug dosing in *all* patient populations or clinical situations
  - In most patients eGFR and CrCl will be similar so can use either
  - Exceptions to the use of eGFR include toxic drugs, in elderly patients and in patients at extremes of muscle mass where calculation of CrCl is recommended.
  - Need to use whichever the reference source used
  - Interpret with caution in amputees, muscle wasting, fluid overload or dehydration, high dietary intake of meat
- **Clinical judgement needed**

Dosing in renal impairment

Drugs requiring maintenance of serum conc. over dosing interval – reduced doses at usual intervals	*Venlafaxine* - use half normal dose if eGFR < 30 ml/min/1.73m^2 *Apixaban* for AF – use half normal dose if CrCl 15-29ml/min
Drugs requiring specific peak concs. – standard dose at extended intervals	Co-*amoxiclav* – 375-625mg every 12 hours if eGFR 10-30ml/min/1.73m^2 (normal dose = 375-625mg every 8 hours)
Using an alternative safer drug	Linagliptin instead of other gliptins Oxycodone instead of morphine

Clinical example

- Mrs RT, 79, presents with confusion.
- U&Es, LFTs, FBC and TFTs normal
- Cr 160micromol/L - has been slowly rising over the past 10 years. eGFR 29 ml/min/1.73m^2
- Has taken digoxin 250 micrograms daily for AF for the past 10 years.
- Digoxin level 3.8 micrograms/L (range 0.8-2).

- **Can you explain what is going on?**

Acute kidney injury (AKI)

AKI is defined as any of the following:

- Increase in serum creatinine by ≥26.5µmol/L within 48 hours; or
- Increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior seven days; or
- Urine volume <0.5ml/kg/hour for six hours

- Seen in 20% of patients admitted to hospital, high mortality rate (up to 80%)
- In approximately two thirds of cases, AKI begins in the community
- Costs of AKI to the NHS £434-620 million/year
- Up to 30% of AKI cases are due to drugs
- Often incomplete recovery of kidney function with many patients developing new or worsening chronic kidney disease (CKD)

Risk factors for AKI

Pre-existing chronic kidney disease
Heart failure
Liver disease
Diabetes
History of AKI
Oliguria
Neurological or cognitive impairment that may limit access to fluids
Hypovolaemia
Use of medicines that impair kidney function
Use on iodinated contrast within the past week
Urological obstruction
Sepsis
Age over 65 years

Including OTC, recreational, herbal

Royal College of General Practitioners

Acute Kidney Injury Toolkit

Table 2: Recognising and Responding to Acute Kidney Injury for Adults in Primary Care

"Think" Cause	"Think" Medication	"Think" Fluids	"Think" Review
History of acute illness? • Think Sepsis • Think Hypotension Intrinsic renal disease (e.g. vasculitis)? • Think Urinalysis Urinary tract obstruction?	Any drugs which could **exacerbate** AKI? Consider withholding: • NSAIDs • Diuretics • Antihypertensive medication Any drugs which may **accumulate** and cause harm during AKI? Any **new** drugs that may be **causing** AKI (e.g. drug-induced interstitial nephritis)?	What is the patient's volume status? If hypovolaemia present: • When did patient last pass urine? • Can patient increase fluid intake? • Does patient have and / or need carer support? • Is admission for IV fluids and monitoring required?	Does patient need admission? If not, when will you review? Have you ensured handover?

https://www.rcgp.org.uk/aki

Acute kidney injury (AKI)

- Withhold medicines which could be exacerbating AKI or are unsafe to use
  - NSAIDs, ACEi/A2RAs, metformin, contrast media, some analgesics, DMARDs
- Doses may need changing according to degree of renal impairment
  - Dosage adjustment should be guided by clinical judgement and monitoring, in addition to published guidance
- Need to consider rapidly fluctuating levels of renal function, changes in volume status and the effects of renal replacement therapy (RRT)
  - In critically ill patients with AKI, serum Cr levels rise 1-2 days after renal insult

Stop/withhold

- NSAIDs
- Potassium-sparing/thiazide diuretics: reduced efficacy, increased risk of adverse drug reactions
- Metformin: avoid if eGFR less than 30ml/min/1.73m^2 – risk of lactic acidosis
- ACE inhibitors/angiotensin II-receptor blockers: depending on indication, if prescribed in heart failure, restart when safe to do so, titrate up and monitor closely. If hypertensive, consider alternative agents
- Lercanidipine: avoid if eGFR less than 30ml/min/1.73m^2
- Methotrexate
- Fibrates and statins: risk of rhabdomyolysis – stop if acute kidney injury develops due to rhabdomyolysis, reduce dose and monitor
- Contrast media

Review dose

- Opioids: avoid MR/XL preparations, use short-acting preparations at the minimum required dose
- Benzodiazepines: reduce dose and monitor for excess sedation
- Penicillins: accumulation leading to CNS toxicity – reduce dose
- Antiepileptic drugs: reduce dose and monitor serum drug levels
- Loop diuretics
- Trimethoprim
- Antianginal drugs, *ie* nitrates and nicorandil: can lead to renal hypoperfusion
- Sulfonylureas: care needed to use the lowest possible dose; gliclazide is metabolised by the liver and can be used in renal impairment
- Gliptins: adjust dose and monitor closely; linagliptin OK to use
- Gabapentin/pregabalin: dose adjustment necessary
- Allopurinol: reduce to 100mg daily

Ongoing monitoring required

- Warfarin
- Ciclosporin
- Digoxin
- Lithium

From prescriber.co.uk
NOT a complete list

Drug induced nephrotoxicity

Pre-renal nephrotoxicity

- Any drug that compromises circulation may induce renal failure
- Drugs particularly associated with renal hypoperfusion and pre-renal AKI include NSAIDs, ACE-inhibitors, ARBs, diuretics
  - Cumulative risk if used concomitantly
- Response to reduced renal blood flow, e.g. in D+V, is to restore GFR through:
  - prostoglandin mediated vasodilation of afferent blood vessels
    - NSAIDs counteract this
  - Renin-angiotensin mediated vasoconstriction of efferent blood vessels
    - ACEi and A2RAs counteract this
- Failure to treat pre-renal causes will lead to ischaemia – acute tubular necrosis (ATN)
  - 80% AKI – pre-renal + ATN

Clinical example

- Mr SL (age 93) admitted to hospital with gout
- Background of chronic kidney disease (serum Cr 140, CrCl 32ml/min)
- Ibuprofen & codeine started on admission
- 3 days later, serum Cr 274 (CrCl 16ml/min)
- Developed severe drowsiness & respiratory depression

Clinical example

- Mr SL (age 93) admitted to hospital with gout
- Background of chronic kidney disease (serum Cr 140, CrCl 32ml/min)
- Ibuprofen & codeine started on admission
- 3 days later, serum Cr 274 (CrCl 16ml/min)
- Developed severe drowsiness & respiratory depression

- **Ibuprofen & codeine stopped**
- **started on naloxone infusion, recovered over 2-3 days**
- **Discharged 2 weeks later, Serum Cr 128**

Intra-renal nephrotoxicity

- **Tubular Necrosis**
  - Occurs if kidney perfusion is not restored
  - Usually caused by combination of factors, including 1+ nephrotoxins (e.g. drugs, sepsis, hepatorenal syndrome, rhabdomyolysis)

- **Interstitial Nephritis**
  - Hypersensitivity reaction following drug exposure
  - Extra-renal symptoms – fever,rash
  - Recovery of GFR occurs, may take up to a year

- **Acute Glomerulonephritis**
  - Immune mediated condition precipitating an inflammatory response in the glomeruli

Post renal (Obstructive) Nephropathy

- Renal tube obstruction caused by
  - crystalluria, e.g. cytotoxics causing deposition of urate crystals in renal tubules
  - clot formation, e.g. as reaction to anticoagulant-induced bleeding

- Antimuscarinic drugs can exacerbate obstruction – avoid

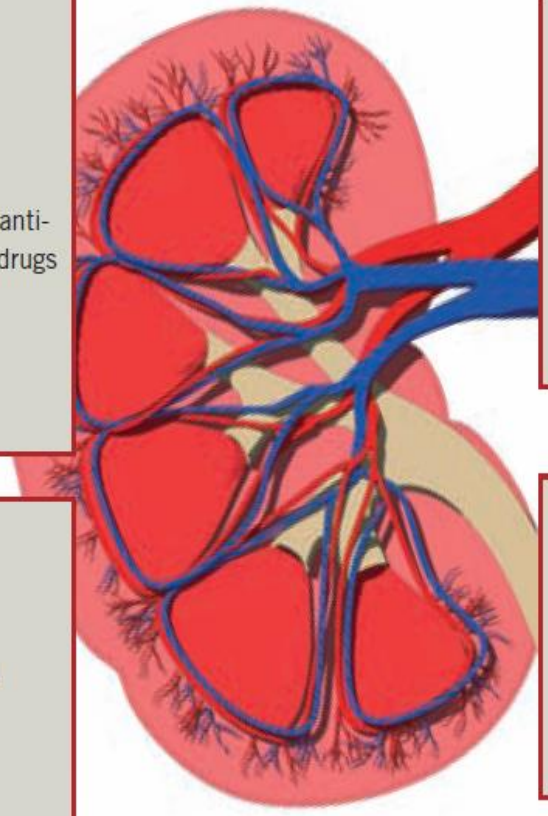
Figure 1: Medicines that can cause acute kidney injury

Intrinsic: acute tubular necrosis

- Aciclovir
- Aminoglycosides
- Amphotericin
- Calcineurin inhibitors
- Cephalosporins
- Cisplatin
- Contrast media
- Ciprofloxacin
- Ethylene glycol
- Foscarnet
- Furosemide
- Gold
- Ifosfamide
- Lithium
- Methotrexate
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Paracetamol
- Rifampicin
- Vancomycin

Intrinsic: acute interstitial nephritis

- Allopurinol
- Aminoglycosides
- Aminosalicylates
- Amlodipine
- Azathioprine
- Beta-lactams
- Captopril
- Carbamazepine
- Diltiazem
- Erythromycin
- Gold
- Interferon
- Isoniazid
- Lithium
- Loop diuretics
- Methyldopa
- Minocycline
- NSAIDs
- Phenobarbital
- Phenytoin
- Proton pump inhibitors
- Pyrazinamide
- Quinolones
- Ranitidine
- Rifampicin
- Sulfonamides
- Thiazide diuretics
- Vancomycin



Pre-renal

- Diuretics
- NSAIDs
- Angiotensin-converting enzyme inhibitors
- Angiotensin-II receptor blockers
- Antihypertensives
- Laxatives (abuse)
- Calcineurin inhibitors (high blood levels)

Post-renal

- Anticoagulants
- Cytotoxic chemotherapy
- Beta-blockers
- Bromocriptine
- Methyldopa
- Methysergide
- Pergolide

Intrinsic: rhabdomyolysis

- Amphotericin
- Barbiturates
- Benzodiazepines
- Colchicine
- Co-trimoxazole
- Fibrates
- Lithium
- Monoamine oxidase inhibitors
- Opioids
- Phenothiazines
- Retinoids
- Theophylline
- Statins

Picture credit: Sebastian Kaulitzki / Dreamstime.com

Information resources

- BNF www.bnf.org
- Electronic Medicines Compendium www.medicines.org.uk
- www.thinkkidneys.nhs.uk
  - Medicines optimisation toolkit for AKI MAY17
  - Plus loads of other useful resources!
- Renal drug handbook (need subscription)
  http://www.renaldrugdatabase.com/
- Pharmacists ☺

- eLFH via https://portal.e-lfh.org.uk/ - e-learning packs on AKI and CKD

General rules

- Always consider renal function when you are prescribing, especially in over 65s
- Single doses – no adjustment needed
- Toxicity usually only a problem for drugs with high renal clearance and narrow therapeutic index
  - Refer to reference sources or ask for advice if unsure
  - Monitor plasma conc. where possible
- Avoid nephrotoxic drugs in pre-existing renal impairment where possible – if use is essential you **must** monitor renal function

General rules

- Review nephrotoxic drugs in patients at risk of AKI, e.g. D&V
- Caution with drugs likely to
  - increase potassium
  - cause fluid retention - NSAIDs, corticosteroids, high sodium content, e.g. some antacids, high dose IV antibiotics
- Remember to restart drugs when/if appropriate

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Any questions?