Drug Dosing

- As a general rule if non-renal clearance accounts for elimination of more than 50% of a drug, then no adjustments need be made to dose or frequency of administration and monitor for signs of accumulation e.g. side effects.
- Dosage of high-risk drugs (e.g. anticoagulants) which are mainly excreted by the kidney (as unchanged drug or active metabolites) may need to be modified to avoid accumulation.
- Renal Drug Database (RDD) provides detailed information on renal dosing.

Loading Dose

- Loading doses are generally unchanged.
- Drugs that require therapeutic levels quickly still require a loading dose as half-life is increased and time taken to reach steady state prolonged for drugs where the metabolism and excretion is slowed in renal impairment.
- For example, antibiotics, a loading dose will enable therapeutic drug levels to be attained quickly. Peak concentrations are also required for optimal bactericidal or bacteriostatic effects, so typically the normal dose is given but less frequently.

Maintenance Dose

- If a drug is normally excreted via the kidneys, its maintenance dose will usually need to be adjusted in patients with renal impairment. There are two ways of doing this:

1. Increase the dosing interval, whilst the dose remains unchanged, e.g. antibiotics;
2. Decrease the dose and dosing interval unchanged e.g. digoxin, a steady plasma concentration is desirable, so dosing interval remains 24 h, and dose is reduced.

- For some drugs, e.g. aminoglycosides, it is necessary to both reduce the dose and increase the dosing interval.

Dialysis Dosing

- If a patient is on dialysis, they have end stage kidney disease (ESKD).
- Don't try to calculate the patient's renal function. Changes in SCr are due to dialysis clearance.
- Assume GFR < 10ml/min and consider timing of doses and removal by dialysis.
- For dosing use RDD - doses for some drugs will differ depending on whether PD, HD or HDF
- HD/HDF most units use high-flux membranes in UK - this option should be used for dosing.

Renal Replacement Technique	Principle of Removal	Typical Effective GFR Achieved (mL/min)
PD	Dialysis and ultrafiltration	5-10
Intermittent HD/HDF	Dialysis and ultrafiltration	250-300 during dialysis < 10 off dialysis
CAVH / CVVH	Ultrafiltration	15-30
CAVHD/CVVHD	Dialysis and ultrafiltration	25-35

Some texts quote supplementary doses to be given after HD/HDF. In practice, it is better to adjust dose timing and dose after the RRT session rather than add in extra doses.

Kidney Transplant

Don't assume transplant patients have normal renal function - most won't. Calculate function as usual and amend drug doses accordingly.

Acute Kidney Injury

It takes time for SCr to get to steady state - no creatinine-based formula will be accurate when kidney function is changing rapidly e.g. AKI. eGFR or C&G must be used with caution taking account of the daily change in serum creatine and other clinical parameters e.g. urine output.

Drug Dosing in Renal Impairment & Dialysis

UKRPG

Many drugs or their metabolites are eliminated from the body via the kidneys. In renal impairment, these drugs will tend to accumulate, leading to toxicity.

Dialysis will replace some of the excretory functions of the kidneys, but is still not equivalent to fully functioning kidneys.

Therefore, it is necessary to amend doses of renally excreted drugs according to the patient's degree of renal impairment or the type of dialysis they are undergoing.

In order to do this, it is necessary to calculate the patient's estimated glomerular filtration rate (eGFR) or their creatinine clearance (CrCl).

ukkidney.org/rpg

Measuring Kidney Function

A measured GFR using exogenous substances filtered by the kidney (e.g. iohexol, 51 Cr-EDTA) provides the most accurate measurement of kidney function. Serum creatinine (SCr) has poorer accuracy; however, it is routinely available and is sufficiently accurate to approximate kidney function in the majority of clinical situations. Cystatin C is another biomarker increasingly used to approximate kidney function. Several equations have been developed to calculate an estimated GFR (eGFR) or calculate CrCl using SCr. These equations are routinely used for drug dosing - it is important to be aware of their limitations.

eGFR Equations

- CKD-EPI 2009 equation (without ethnicity coefficient) is the recommended method for estimating GFR and calculating drug doses in most patients with kidney disease.
- CKD-EPI estimates GFR from SCr, age and sex and is more accurate than the MDRD Study equation, particularly in people with higher levels of GFR.
- CKD-EPI 2021 should not be used until validated in UK cohort.

CrCl - Cockcroft & Gault Equation (C&G)

$$\text{CrCl} = \frac{[140 - \text{Age (years)}] \times \text{Weight (kg)}}{\text{Plasma creatinine (μmol/L)}}$$

- Males x 1.23; Females x 1.04
- For obesity use adjusted body weight (i.e. If patient's weight is > 15% over IBW or BMI > 25). Poor evidence in this area means it can be helpful to consider approximations based on IBW, ABW as well as adjusted body weight (MDCALC).

Standardisation of Kidney Function Measurement

There is poor standardisation of SCr and eGFR laboratory reporting in the UK – to the extent that clinically significant inaccuracy in GFR estimation may occur, affecting prescribing practice as well as diagnosis and CKD staging. The UKKA have released a patient safety alert, and UK labs are working towards standardising all SCr measurements by enzymatic process and all eGFR reporting by CKD-EPI 2009.

Equation Choice for Drug Dosing

eGFR is more accurate than C&G for approximating renal function and newer drugs are recommended to be developed using eGFR with standardised SCr. However, drugs were previously developed without this standardised approach, often using C&G with a range of SCr assays. For these reasons, it remains difficult to endorse a single approach for dosing drugs, and there are situations where it is helpful to consider more than one equation.

Always remember the following when approximating kidney function using SCr:

- In most clinical situations using eGFR for drug dosing is appropriate – remembering to adjust for BSA if extremes of body weight.
- eGFR is standardised to a body surface area (BSA) of 1.73m^2 and risks drug dosing errors for people at extremes of body weight. An 'Absolute GFR' (eGFR x BSA/1.73) must be calculated when determining drug doses in patients whose BSA differs significantly from 1.73m^2 e.g. BMI < 18kg/m^2 & BMI >40kg/m^2
- There are situations where it is important to consider C&G CrCl in addition to eGFR – examples of high-risk drugs where this is done routinely include: anticoagulants (DOACs, LMWHs fondaparinux), valganciclovir, acyclovir/valaciclovir, co trimoxazole.
- C&G CrCl is an alternative to calculating 'Absolute GFR' for patients at extremes of body weight. Remember to use an ideal or adjusted body weight in overweight patients.
- MHRA provides details of other situations where a C&G CrCl should be considered e.g. elderly patients (age>75yrs).
- SCr derived measurements are not accurate in periods of rapidly changing renal function (e.g. acute kidney injury AKI).
- SPS provides summary on calculating kidney function.

High-Risk Drugs

- Caution is required for all drugs normally excreted by kidney – but particular care where drug excreted by kidney and high risk of adverse effects in overdose – e.g. anticoagulation, opioid analgesics, aciclovir/valaciclovir, narrow therapeutic index drugs, e.g. digoxin, gentamicin.
- Drugs metabolised by the liver but with pharmacologically active metabolites that are excreted via the kidneys e.g. morphine
- Drugs known to have direct effects on structures of the kidney e.g. NSAIDs, methotrexate, certain chemotherapy.

Drug Accumulation

Some drugs have direct effects on the kidney and can increase risk of kidney damage in renal impairment when they accumulate e.g. tacrolimus, gentamicin. However, many drugs will cause adverse effects in other body systems when they accumulate e.g. cephalosporins, penicillins, carbapenems → grand mal fits, opioids → respiratory depression & sedation, aminoglycosides → nephrotoxicity & ototoxicity, allopurinol → bone marrow suppression.