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Part 1 Introduction

Chapter 1

The Basics of Safe Drug Use

Yogini Jani

Here, 'safe drug use' refers to your prescription and administration, not recreational use. In this regard, there are a few 'golden rules' which will keep you out of trouble (and court!).

Ready?

You can't be expected to 'know it all' let alone remember it all. So seek references!

a. Find local policies/protocols in your hospital formulary and use them.
b. Check the BNF when in doubt. It is now available online and as an app too (https://bnf.nice.org.uk). Remember that, as well as dosing, it will tell you indications, contraindications, interactions, side effects, use in hepatic and renal failure, and use in pregnancy. It also includes National Institute of Health and Care Excellence (NICE) guidelines, other disease management guidelines (e.g. British Thoracic Guidelines on acute asthma), and an 'important safety advice section' that highlights warnings issued by the Commission on Human Medicines (CHM) or the Medicines and Healthcare products Regulatory Agency (MHRA).
c. Ask your pharmacy for help as a matter of routine, not just when 'it's all gone wrong'!
d. If the organisation is using electronic prescribing systems, many standard reference sources such as the BNF online, local protocols and national guidelines may be available as links: learn to use them effectively.

Steady…

Whether your hospital uses a paper chart (this is becoming rare but always good to know your way round one in case of technology failures!), or a funky electronic system, there will be separate prescribing sections. These include sections for one off 'STAT' doses of drugs, regular medications, as required 'PRN' drugs, infusions and intravenous fluids. There may also be supplementary charts or separate sections for 'specialist' items, e.g. total parenteral nutrition, anticoagulation and chemotherapy.

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Beware

- ... of where you write/order your prescription! If incorrectly done, it may mean your patient does not get the drug, or you end up correcting lots of charts.
- In electronic systems, take care with default start times and dates – for once a day doses, the system may schedule the first dose for the next available time-slot – which may be too late for your patient.

GO!

You have now decided what to prescribe and at what dose, and have chosen which section to write/order the prescription. Now use 'SICKLy' tips to avoid mistakes:

Simplify. Try NOT to give drugs at all. All drugs have side effects and are hazardous. Every now and then, the drug you give will contribute (directly or indirectly) to a death. Did you know that the World Health Organization estimates an annual cost of $42 billion due to preventable medication harm?

Do you really have to give it? Will the green spit or sore throat not get better on its own? Is the cough so bad that codeine linctus and its side effects of constipation and drowsiness are worth it? Can you do anything that avoids drugs? e.g. reassurance, ear plugs if noise is keeping a patient awake, fruit and coffee for constipation?

Try to STOP (or 'deprescribe') a drug every time you review a chart.

Wherever possible, seek the 'once-a-day' drug from a class. Compliance will be better on discharge and the fewer the 'prescribing events' the fewer things that can go wrong!

Interrogate your patient and their charts: *Are all their allergies documented?* And what does the patient mean by 'allergy' to toxocillin? That they got a runny nose, or a rash or 'full blown' anaphylaxis? Were you just about to prescribe a drug that will make their skin peel off?

What is your patient's weight? You will need to know this to prescribe certain drugs, e.g. low molecular weight heparin, intravenous paracetamol and once daily gentamicin. Importantly, has the patient's weight changed significantly since the drug was prescribed, thus changing the prescribed dose?

What is your patient's height? This is needed to calculate surface area or ideal/excess body weight, which are required for gentamicin dosing and chemotherapeutics.

Clarify. Be clear in *writing/ordering* a prescription. Do not rush. Is there ANY chance that your script will be misread if on paper? Or that you may MIS-SELECT from an alphabetical electronic list of similar names?

Be clear in *reasoning*. Add comments where needed e.g. 'patient has been on sleepazepam for 20 years and withdraws without it: please give'.

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Be clear with *timing*, in particular, start and stop times. We have all heard of patients still taking a loading dose of amiodarone daily, until their lungs are ruined with fibrosis. Clearly indicate on the chart when you want the course to be changed. Prescribe the 'reducing doses' for a full course, so that when you are next doing 'days' you don't still find the patient on 60 mg prednisolone 5 weeks on!

Check. Check *doses* etc. of unfamiliar drugs before prescribing. Electronic systems may highlight these as pop-up alerts. Resist the temptation to hit enter too quickly – make sure you READ what it says!

Check for *interactions* with the other charted drugs.

Check the doctor was correct in what they wrote, if you are *administering*.

Check everything you do at least twice. With intravenous drugs, NEVER be lazy. When tired, you can read what you expect to see. Ask someone else to check the ampoule or vial against the prescription ALWAYS!

Know. Have a basic understanding of the class of drug you are giving. Know a line or two about how it works. This is your safety lock: it allows you to hear alarm bells, nudging you to recall a drug interaction or side effect. Back this up revising from time to time the basic side effects and interactions of a drug and its class in a bigger textbook. If your patient does react, then manage them, but think about future treatment: is it an allergy (confirmed by testing) or an intolerance (side effect that may be managed in case of benefit/risk)? Document the reaction so that it can be communicated to the whole team and eventually the GP, and educate the patient about future implications.

Think **L**evels! Consider factors that might alter drug levels, e.g. age, disease, other drugs? Consider if the drug you are about to prescribe needs its levels monitored? Are you sure? *Check*. Call pharmacy. Call microbiology. Call a colleague. But *do call!* If yes, be clear about when levels should be taken, and how often. And ensure they are taken and acted upon. Put some fail safes in – mark the chart 'not to be given until Dr has reviewed levels' or 'do not give until INR has been seen'. On electronic systems, you can 'prescribe' the levels too, and the whizzier e-prescribing systems can be set up with rules so the dose cannot be given unless the result is available. And, lastly, think who will continue to review their levels when they are discharged? Have you booked them into anticoagulant clinic?

So, familiarise yourself with the chart and back yourself up with some information. Then, think:

SICKLy:

Simplify the chart (fewer drugs, fewer doses).

Interrogate the notes/charts/patient for contraindications, allergies and interactions. Take note of and act on electronic alerts.

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Clarify your chart. Be clear with your writing/ordering, reasoning and timing.

Check doses, interactions and all ampoules or vials.

Know your drug classes, their mechanisms and major side effects/interactions.

Levels: think about factors that alter levels, and the need for monitoring them.

Finally, congratulations! Your patient has survived! Now safely DISCHARGE them!

1. Note the patient's discharge medications carefully, following the rules as above.
2. Mark clearly any changes from their admission medications, and include reasons for these changes.
3. Ensure the patient is aware of these changes: drugs will only work if the patient actually takes them – correctly.
4. Organise necessary follow-up, e.g. repeat phenytoin or INR levels, GP appointment after completion of steroid reduction for acute asthma etc.

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Part 2 Prescribing for Patient Groups

Chapter 2

Prescribing in Renal Disease

Dipty Joshi

Don't *cause* renal failure!

Kidneys are desperately sensitive to damage by drugs: fully 20% of acute kidney injury (AKI) episodes are drug-induced! Be afraid. Be *very* afraid. And then take care:

- Identify patients at risk and, if possible, eliminate these risk factors.
- Avoid potentially nephrotoxic agents wherever possible.
- Adjust drug doses, where necessary, in all those with pre-existing renal impairment, as drug accumulation and toxicity can quickly develop.

Many drugs are potentially nephrotoxic, and the list is too long to remember. However, high-risk *classes* to **AVOID** are as follows:

ACE Inhibitors and ARBs

ACE inhibitors and ARBs lower glomerular filtration pressure and can aid tubular uptake of other nephrotoxic drugs. Take care in patients with pre-existing renal disease, those who are dehydrated, those taking other potentially nephrotoxic drugs and those with possible renal artery stenosis. If worried, monitor blood pressure and biochemical markers of renal function carefully.

Iodinated Contrast Media/Dye

Risk is particularly high in patients with pre-existing renal impairment and in those with dehydration. In 50% of diabetics with impaired renal function, renal function declines further after use of radiocontrast agents. Hydration with a balanced salt solution (Hartmann's/Ringer's lactate) is a key preventative strategy. Hydration with sodium bicarbonate 1.26% can help in high-risk patients.

Antibiotics

Antibiotics can be directly tubulotoxic, or can cause allergic interstitial nephritis or crystallisation within the renal tubules. Aminoglycosides are a common

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culprit: even with proper dose adjustment (see Chapter 37 – Therapeutic Drug Monitoring) there is no guarantee of safety and nephrotoxicity can still occur at therapeutic levels. Penicillins, cephalosporins and quinolones are also common culprits.

Lithium

Careful monitoring of levels is crucial.

NSAIDs and COX-2 Inhibitors

Risk rises with dose. If worried, think of alternatives (see Chapter 23 – Analgesia).

You should especially **AVOID** using such classes in combination: gentamicin + cephalosporin in the infected renal stone patient is bad enough but add diclofenac for the pain and …!

TOP TIPS to Avoid Drug Toxicity

- Don't exceed the recommended dose.
- For patients at risk of AKI, reduce the dose, concentration and/or rate of administration.
- Where necessary, monitor drug levels closely (e.g. vancomycin or gentamicin).
- Tailor the drug therapy to the individual needs of each patient with renal insufficiency. Some patients might still have some residual function left, which you will want to try to preserve for as long as possible.
- Periodic monitoring of renal function and urine output is particularly important in patients with renal impairment or at risk of developing AKI.

IF IN DOUBT, ASK YOUR HOSPITAL PHARMACIST!

Before choosing an appropriate drug and dosage schedule, the severity of renal impairment must be assessed. This is done by estimating the GFR.

Treatment of the Patient with Known Chronic Renal Impairment

Ok, so now the patient has presented with chronic renal failure (CRF). What drugs might they need? Here is a rough guide!

- Hypertension – a slight decrease in BP can have a significant effect in rescuing the patient's renal function. For example, ACE inhibitors can reduce the rate of loss of function, even if the blood pressure is normal but the protein:urea ratio is high.
- Oedema – treatment with high doses of loop diuretics (e.g. furosemide 250 mg–2 g/day ± metolazone 5–10 mg/day) might be required.

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- Renal bone disease – give phosphate binders (e.g. sevelamer) and vitamin D analogues (alphacalcidol) and treat as soon as there is an increase in parathyroid hormone.
- Dietary advice – aim to restrict sodium intake as this will help to control BP and prevent oedema. Restrict potassium if there is evidence of hyperkalaemia and acidosis, in which case treat with bicarbonate supplements. Reduce dietary phosphate intake.
- Anaemia – treat with erythropoietin. Give iron if deficient.
- Hyperlipidaemia – this will increase the risk of cardiovascular disease and contribute to renal insufficiency. Use statins as first line.

Do your sums!

Drug doses can be adjusted according to the patient's estimated (or measured) creatinine clearance (CrCl). The most accurate method of determining CrCl is to gather urine over 24 hours, and then use the following equation:

$$CrCl = UV / Pt$$

where:

U = urinary creatinine concentration (mmol/L)
V = volume of urine (mL)
P = plasma creatinine concentration (mmol/L)
t = time (minutes)

A quicker and less cumbersome method that is widely used to measure the adult plasma creatinine concentration (and hence renal function) is with the Cockroft and Gault equation:

$$CrCl = \frac{G \times (140 - age\ in\ years) \times weight\ in\ kg}{serum\ creatinine\ (mmol/L)}$$

where:

G = 1.04 (females) or 1.23 (males)

Height and body weight are critically important to calculate drug dosages – particularly in obese or oedematous patients, use ideal body weight.

A point to remember about the Crockroft and Gault equation is that it merely provides an approximation of creatinine clearance, particularly when the clinical setting is dynamic and the renal function might be changing on a daily basis. The equation is useful when renal dysfunction is stable. However, in AKI, creatinine concentrations might not have reached steady state and so might not reflect the true functional capacity of the kidneys.

As a broad classification, renal impairment is divided into three groups for prescribing purposes (Table 2.1).

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Table 2.1 Renal impairment classification groups

Grade	GFR (mL/min)	Serum creatinine (mmol/L)
Mild	20–50	150–300
Moderate	10–20	300–700
Severe	<10	>700

Armed with this classification, you are now in position to choose the right dose from the Table 2.2.

Table 2.2 Drug doses in renal impairment

Drug	CrCl (mL/minutes)	Dose
Aciclovir PO	20–50 10–20 <10	Normal Herpes simplex: 200 mg QDS to TDS Herpes zoster: 400–800 mg TDS Herpes simplex: 200 mg BD Herpes zoster: 400–800 mg BD
Aciclovir IV	25–50 10–25 <10	5–10 mg/kg BD 5–10 mg/kg BD 2.5–5 mg/kg BD
Allopurinol	20–50 10–20 <10	200–300 mg OD 100–200 mg OD 100 mg OD/alternate day
Amikacin IV	20–50 10–20 <10	5–6 mg/kg BD 3–4 mg/kg BD 2 mg/kg every 24–48 hours
Amoxicillin PO/IV	20–50 10–20 <10	Dose as per normal renal function Dose as per normal renal function 250 mg TDS
Amphotericin IV	<50	Seek advice
Anakinra	30–50 10–30 <10	Dose as per normal renal function 100 mg on alternate days 100 mg on alternate days
Apixaban	30–50 15–30 <15	Dose as per normal renal function. Use with caution AF: 2.5 mg twice daily Use with caution Manufacturers advise to avoid

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Drug	CrCl (mL/minutes)	Dose
Avanafil	30–50 10–30 <10	Dose as per normal renal function Use with caution Use with caution
Azathioprine	20–50 10–20 <10	Dose as per normal renal function 75–100% 50–75%
Benzylpenicillin IV	20–50 10–20 <10	Dose as per normal renal function 75% 20–50%
Bisoprolol	20–50 10–20 <10	Dose as per normal renal function Dose as per normal renal function 1.25–10 mg OD
Cariprazine	30–50 <30	Dose as per normal renal function Cariprazine has not been evaluated in patients with severe (CrCl < 30 mL/min) renal impairment
Cefotaxime IV	20–50 10–20 <10	Dose as per normal renal function Dose as per normal renal function Load with 1 g then BD dose at same frequency
Ceftazidime IV	31–50 16–30 6–15 <5	1 g BD[a] 1 g OD[a] 500 mg–1 g OD[a] 500 mg–1 g 48-hourly[a]
Ceftriaxone IV	10–50 <10	Dose as per normal renal function Use with caution in patients with severe renal impairment as well as hepatic insufficiency. In severe infection, dose at 1 g OD and increase to 2 g if necessary.
Cefuroxime IV	20–50 10–20 <10	750 mg–1.5 g TDS 750 mg–1.5 g TDS to BD 1.5 g OD
Chloral hydrate	20–50 10–20 <10	Dose as per normal renal function 500 mg nocte Avoid
Ciprofloxacin	20–50 10–20 <10	Dose as per normal renal function 50% of normal dose 50% of normal dose

(cont.)

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Table 2.2 *(cont.)*

Drug	CrCl (mL/minutes)	Dose
Clarithromycin	20–50 10–20 <10	Dose as per normal renal function PO: 250–500 mg BD to OD IV: 250–500 mg BD PO: 250 mg BD to OD IV: 250 mg BD
Clevidipine	10–50	Dose as per normal renal function
Clindamycin	10–50	Dose as per normal renal function
Clonidine	10–50	Dose as per normal renal function
Co-amoxiclav	30–50 10–30 <10	Dose as per normal renal function PO: Dose as per normal renal function IV: 1.2 g BD PO: 375 mg TDS IV: 1.2 g STAT followed by 600 mg to 1.2 g OD
Co-codamol/ Co-dydramol	20–50 10–20	Dose as per normal renal function 75–100% of normal dose
Co-trimoxazole PO/IV	>25 25–15 <15	Dose as per normal renal function Normal dose for 3 days, then half standard dose To be given if haemodialysis facilities are available. Normal dose for 3 days than half standard dose
Colchicine	20–50 10–20 <10	Reduce dose or increase dosage interval by 50%. Reduce dose or increase dosage interval by 50%. 500 mcg 3–4 times a day; maximum total dose of 3 mg
Dabigatran	30–50 <10–30	VTE prophylaxis: 75 mg within 1–4 hours of completed surgery and thereafter 150 mg once daily; 75 mg if also on CYP450 inhibitor AF/DVT/PE: 110–150 mg twice daily Contraindicated
Dapagliflozin	20–50	Avoid
Degarelix	20–50 <10	Dose as per normal renal function Dose as per normal renal function. Use with caution
Doxazosin	<50	Dose as per normal renal function
Doxycyline	<50	Dose as per normal renal function
Dulaglutide	10–50	Dose as per normal renal function
Dutasteride	10–50	Dose as per normal renal function

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