Medicines in renal disease

After completing this tutorial, you will be able to:

- Make decisions about appropriate choice and dose of medicines in patients with renal impairment.
- Assess and calculate renal function.
- Describe the main types of renal replacement therapy and how they may affect drug therapy.
- Explain mechanisms by which medicines may adversely affect the kidney.

Why this subject matters…

Renal impairment is common in hospitals and pharmacists are often asked to help choose medicines that are considered safe in these patients, or to advise on dose reduction.

Prescribing in patients with renal failure is not an exact science. The practical knowledge of clinical professionals combined with some published evidence, and the basic principles of drug clearance help to guide decision-making.

You may find it helpful to refresh your knowledge of kidney function before reading on.

Medicines and the kidneys

The way that a medicine behaves in the body can be strongly influenced by the kidney and any degree of reduced function it has. The kidney affects medicines in three principal ways:

1. Excretion

Most systemically administered drugs are eliminated at least partly by the kidney, even if it is only a small proportion of the administered dose. However, for some drugs, the kidney is the major site for elimination of unchanged drug and these are particularly liable to require careful dose adjustment in patients with renal dysfunction to prevent accumulation.

Examples of drugs principally eliminated unchanged by the kidney include:

Aciclovir	**Cefotaxime**	**Ciprofloxacin**	**Digoxin**
Electrolytes	**Fluconazole**	**Gentamicin**	**Lithium**
Meropenem	**Methotrexate**	**Pamidronate**	**Vancomycin**

In addition, there are drugs with therapeutic activity at least partly dependent upon metabolites that are excreted unchanged by the kidney. An example is allopurinol, which has an active metabolite called oxipurinol which works in the same way as the parent drug. Some drugs have toxic metabolites that are eliminated renally. For example *nor*-pethidine, a major metabolite of pethidine, can accumulate in renal failure to cause CNS toxicity such as convulsions. The high incidence of adverse drug reactions seen in patients with renal failure may be explained in part by the accumulation of drugs themselves or their metabolites.

The effectiveness of some drugs may be reduced with advancing renal impairment such as nitrofurantoin; inadequate urine concentrations may result in treatment failure when the eGFR is <45mL/min/1.73m^2. Read the MHRA's guidance on the subject here.

2. Distribution and bioavailability

Renal insufficiency frequently alters the **volume of distribution** of drugs. Oedema or ascites may increase the apparent volume of distribution of highly water-soluble drugs (e.g. gentamicin). Higher doses may be needed to produce the desired therapeutic effect. Conversely dehydration or muscle wasting may result in unexpectedly high plasma concentrations of drugs.

Predicting the clinical consequences of **altered protein binding** in renal insufficiency is difficult. Plasma protein binding is decreased when plasma urea levels are high (uraemia) due to altered albumin affinity for the drug. Patients with chronic kidney disease may also have hypoalbuminaemia. Decreased binding results in more free drug being available at the site of action but a shorter half-life as more free drug can be metabolised and/or excreted.

Patients with **uraemia** are often more susceptible to drug effects (e.g. increased effect of CNS depressants due to increased permeability of the blood brain barrier).

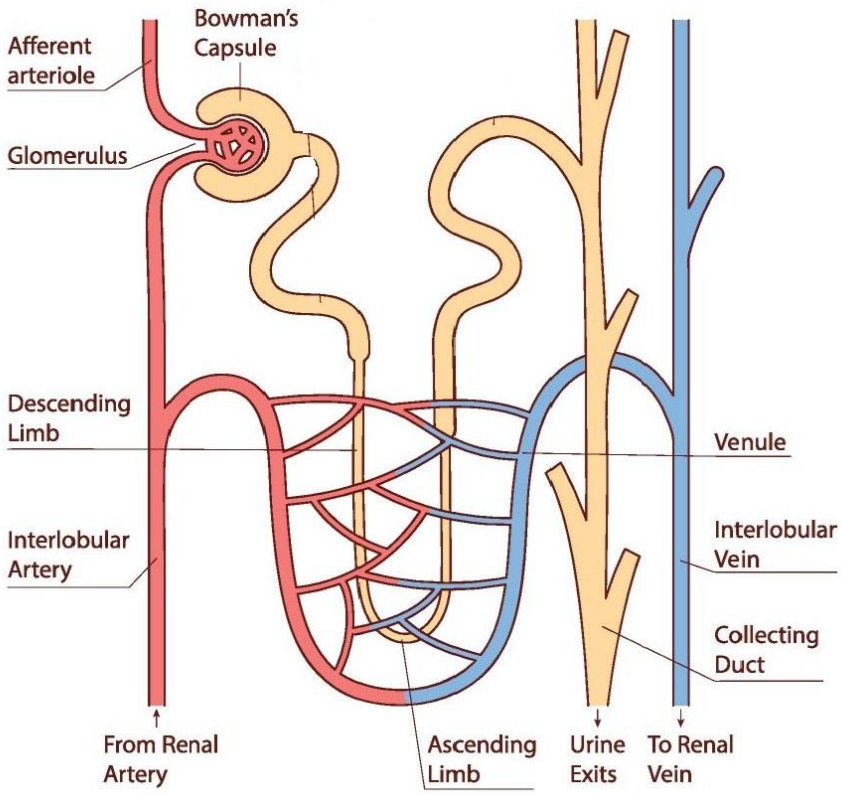
3. Metabolism

The kidney is a site of metabolism in only two clinically important examples. The conversion of 25-hydroxycholecalciferol to the *active* form of **vitamin D** called 1,25-dihydroxycholecalciferol (calcitriol) takes place in the kidney, and this process is often impaired in patients with renal failure. Patients with renal disease requiring vitamin D supplementation should be given the hydroxylated derivatives: either alfacalcidol (1-alpha-hydroxycholecalciferol) or calcitriol.

The kidney is also a major site of **insulin** metabolism and so patients with diabetes and renal failure may require less insulin.

Assessing renal function

The extent of accumulation of drugs in renal impairment depends on the degree of dysfunction, the normal route of excretion, and the dose. Before a drug and dose schedule can be chosen, the severity of renal function must be established. To refresh your memory about how the nephron works, watch this short video.



Structure of a nephron

Renal function is assessed by measuring or estimating **glomerular filtration rate** (GFR), which reflects the number of functioning glomeruli. The GFR can be estimated by looking at the rate at which the body clears one of its own waste products – creatinine. This is called the **creatinine clearance** (CrCl). Using serum creatinine to calculate CrCl assumes that renal function and serum creatinine are stable.

Creatinine clearance is calculated as follows using the Cockcroft-Gault equation:

CrCl (mL/min) = F x (140 – age) x (weight in kg)/plasma creatinine (micromol/L)

where F = 1.04 in females and 1.23 in males. Weight should be ideal body weight (IBW) particularly in oedematous patients and patients with ascites. For patients who are obese, IBW can be used but some experts have suggested that an adjustment factor of 40% be applied to the patient's excess weight over their ideal weight.

The Cockcroft-Gault equation should not be used in children, pregnancy or rapidly changing renal function. Use in patients with low muscle mass may lead to an overestimation of renal function; conversely use in patients with high muscle mass may lead to an underestimation of renal function.

Alternative methods of expressing renal function include the **Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)** or the **Modification of Diet in Renal Disease (MDRD)** formulae to give estimates of GFR (known as **eGFR**). There are similarities with the Cockcroft-Gault equation, but important differences include the assumption that patients are of average weight and build and so are of average surface area (1.73 square metres).

These equations have limitations similar to the Cockcroft-Gault equation, and should not be used for patients who are at extremes of weight, are pregnant, or for children. In addition the MHRA have advised that eGFR should **not** be used to calculate the dose for patients taking **renally excreted drugs with a narrow therapeutic range, nephrotoxic medicines or direct-acting oral anticoagulants**; a CrCl calculated using the Cockcroft-Gault equation should be used.

Actual GFR may be calculated from eGFR using the following equation:

Actual GFR = eGFR x BSA/1.73

The CKI-EPI, MDRD and Cockcroft-Gault equations may produce **different estimates of renal function and are not interchangeable.** Most published information on drug elimination in renal failure is usually stated in terms of CrCl using the Cockcroft-Gault equation.

In the UK, clinical laboratories should report eGFR and serum creatinine, so that you can calculate CrCl using the Cockcroft-Gault equation if required.

It is important to remember that the normal process of ageing involves the loss of nephrons and therefore it is reasonable to assume that all **elderly patients** have some degree of renal impairment.

Plasma urea can be used to estimate renal function, but its production is more variable than that of creatinine and is therefore not reliable.

Renal replacement therapy

Renal replacement therapy (RRT) is indicated when renal function is so poor that the kidneys are barely operational. RRT is used in the management of **acute kidney injury (AKI)** to remove toxins, excess fluid and to correct biochemical disturbances. It also forms part of ongoing regular care in patients with **end-stage chronic renal failure** where kidneys have ceased to function permanently.

There are **four main types** of RRT in common use:

- Haemodialysis (**HD**)
- Peritoneal dialysis (**PD**)
- Haemofiltration (**HF**)
- Haemodiafiltration (**HDF**)

In HD, blood is presented to one side of a membrane, and a dialysis solution is presented to the other side. This encourages toxins to leave the patient's blood and enter the solution by **diffusion**. Fluid is removed by a process called **ultrafiltration**. In PD this membrane is the patient's peritoneum. There are two kinds of PD. Continuous Ambulatory Peritoneal Dialysis (CAPD) involves regularly instilling fluid into the abdomen during the day, and later draining it. Automated Peritoneal Dialysis (APD) is the same basic process except that a machine delivers and then drains the fluid at night while sleeping.

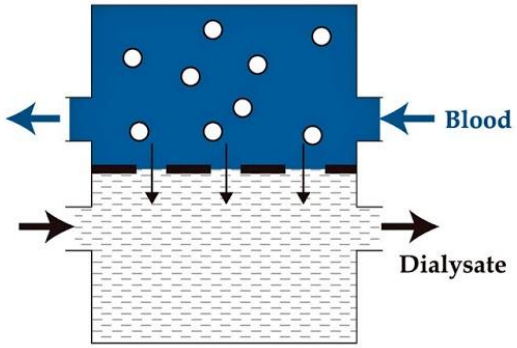
In HF, blood is presented to one side of a membrane, but there is no solution on the other side: pressure is used to drive water and solutes through the membrane by **convection** and this 'filtrate' is then removed. HDF is a hybrid of HD and HF.

HD is usually performed intermittently (e.g. three times a week) and on an outpatient basis. HF and HDF are used typically in intensive care patients where they run continuously.

A detailed discussion of the differences between techniques is beyond this tutorial, but the diagram on the next page compares them. If you want to learn more and have time, you may find this video helpful. Do note it discusses continuous HD; as above, in the UK in a general setting, you are probably more likely to encounter intermittent HD.

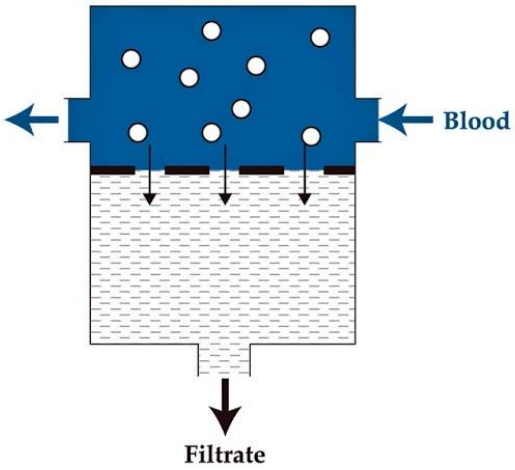
NHS Choices has information for patients about dialysis, and you can also see a detailed diagram of a typical method by which haemodialysis is organised on page 8.

Haemodialysis



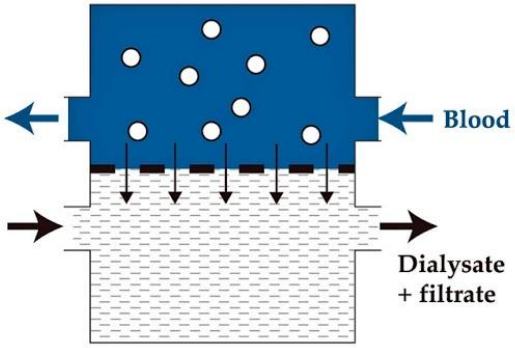
- Intermittent HD may be low or high-flux.
- High-flux dialyser membranes have larger pores compared to low-flux.
- An intermittent process – e.g. 3 short (3-5 hours) sessions per week.
- Fast flow rate using a pump enabling processing of large volume of blood.
- This can cause haemodynamic instability.
- Removes less fluid compared to HF as it is intermittent.
- Dialysate flows in the opposite direction to the blood.
- Rapid clearance of low molecular weight solutes by diffusion.
- Speed and clearance of solutes determined by molecular size, osmotic pull across membrane and flow rate.

Haemofiltration



- Uses highly-permeable membrane.
- Slow flow rate of blood compared to IHD but as it is a continuous process, larger volumes of fluid are removed.
- Slow flow rate also provides better control of fluid balance.
- Usually used in a critical care setting.
- Pressure drives water and solutes from the blood across the membrane to the filtrate.
- Solute removal by convection (''solvent drag'').
- Dialysate is not used.
- Larger pores in the membrane than in IHD so clears comparatively more medium molecular weight solutes (<5, 000 up to 50, 000 daltons).

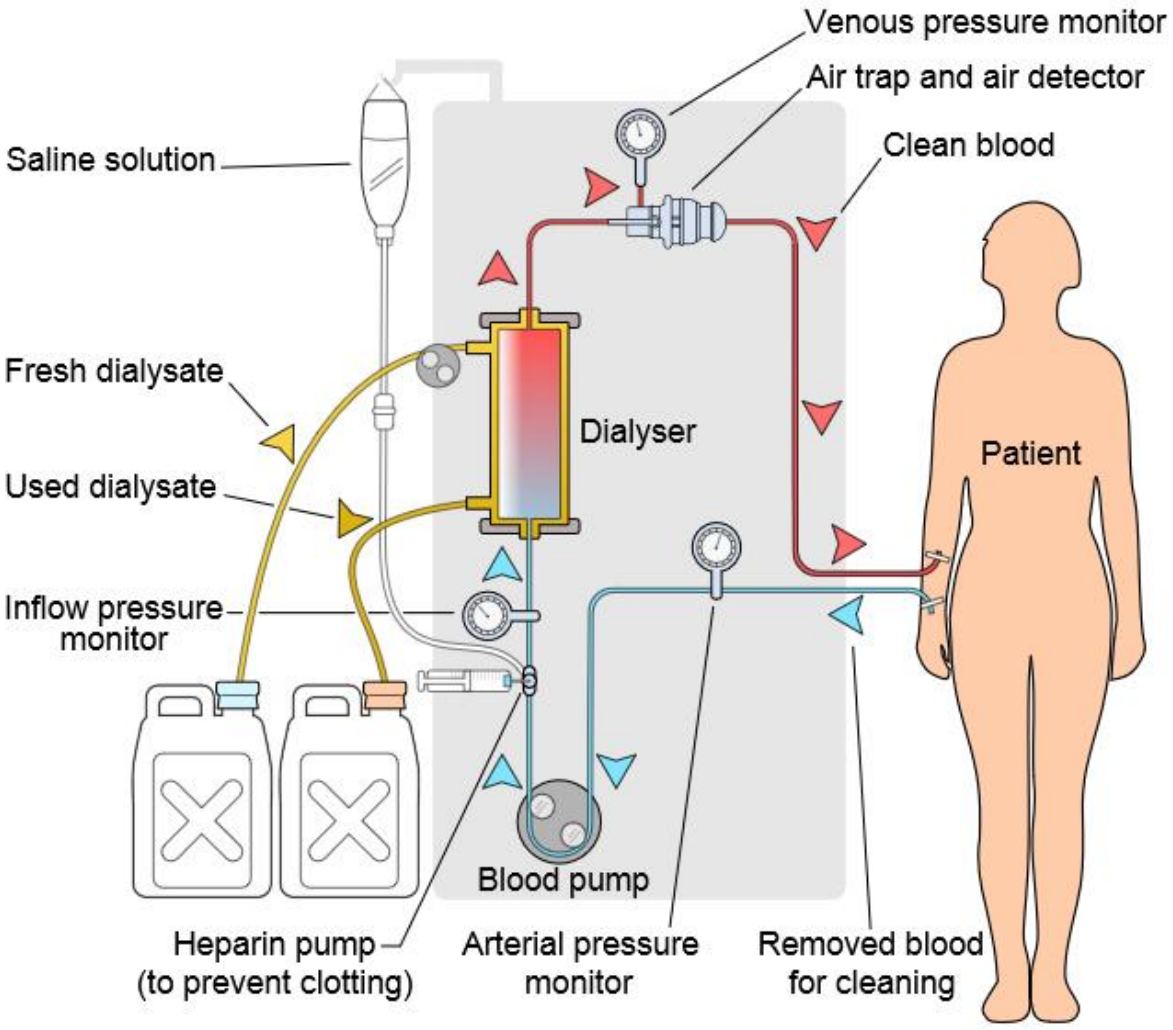
Haemodiafiltration



- Uses a high-flux membrane that allows diffusion and convection.
- Adopts elements of haemodialysis and haemofiltration.
- Dialysate flows in the opposite direction to the blood.
- It is a continuous process in a critical care setting.
- It is the most effective at removing solutes (molecules <500 up to 50, 000 daltons).

Organisation of haemodialysis

This illustrates the flow of a patient's blood through the haemodialysis machine.



Courtesy of Yassine Mrabet, Wikimedia Commons

Drug removal by RRT

Factors affecting the removal of a drug from the blood by RRT include:

- Protein binding – highly protein bound drugs are not generally removed by RRT.
- Molecular weight – very large molecules are less likely to be removed than smaller ones.
- Water solubility – dialysis solutions are aqueous so water-soluble drugs enter them preferentially. Lipid-soluble drugs tend to have larger volumes of distribution and so concentrations in plasma are comparatively small.
- Flow rate, and the chemistry and surface area of the membrane.

Dose adjustment to allow for RRT is only necessary for drugs that require dose adjustment because of the presence of renal failure. However, given the major differences between the forms of RRT, it is vital to know which type a patient is receiving before offering any advice. In general, the following basic rules apply:

- No RRT is as effective as the normal kidney – so doses used will never be larger than those recommended in normal renal function.
- Drugs which are cleared by the kidneys are usually dialysed, and vice versa, although there are some anomalies.

An outpatient attends his regular haemodialysis session
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- If there are no specific guidelines on how to dose a drug in a particular RRT system then for HD and PD use a dose as would be used for a GFR of less than 10mL/min (i.e. severe failure). In practice, although it is recognised that HF is not as effective at drug clearance than HDF, intensive care units tend to dose patients on either as if they have a GFR of about 15-25 mL/min, i.e. as for moderate renal impairment. There is no need to calculate a patient's CrCl from their serum creatinine to guide drug dosing if they are

receiving RRT.

- Always aim to give drugs *after* any session of HD otherwise the drug could be removed before it has time to act fully. For HF or HDF use in a critical care setting, there is no need to schedule doses around RRT sessions as both are continuous processes.

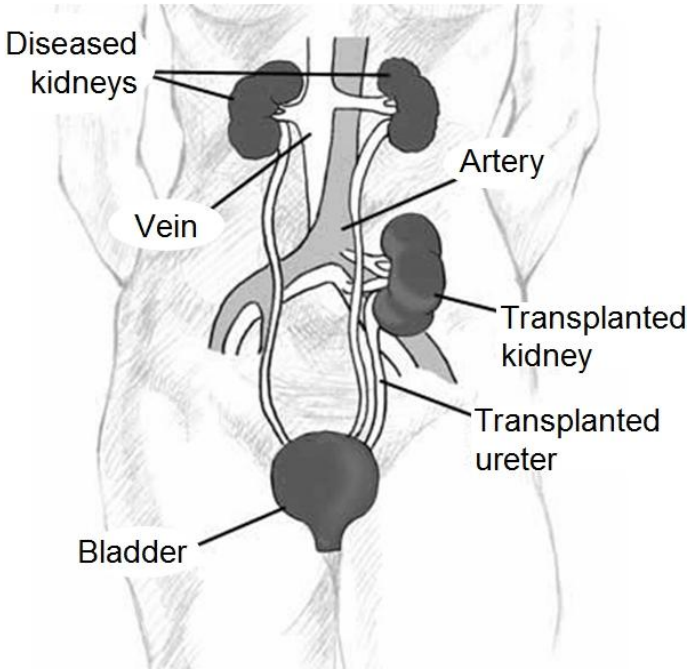
After a renal transplant

Once a kidney transplant has stabilised, patients should ideally have a reasonably healthy GFR of greater than 40mL/min. Consequently, dose reduction of drugs that are renally-eliminated is not usually needed. However, graft function does tend to diminish with time, so it is imperative to check renal function regularly.

Many of the immunosuppressants taken post-transplant interact with a variety of drugs and you should **always check for interactions**. Common immunosuppressants used to prevent transplant rejection include:

Ciclosporin	**Tacrolimus**	**Mycophenolate**
Sirolimus	**Azathioprine**	**Steroids**

Remember that ciclosporin and tacrolimus should be prescribed by their brand name.



A transplanted kidney is positioned lower in the pelvis than the patient's own kidneys and attached to the common iliac artery and vein

Courtesy of http://kidney.niddk.nih.gov/kudiseases/pubs/transplant, Wikimedia Commons

Bear in mind that transplant patients only have one working kidney, and it may not have perfect function, so it is vital to avoid all medicines that may impair kidney function (e.g. NSAIDs).

Medicines that impair kidney function

Three common mechanisms of drug-induced renal impairment are:

- Reduced GFR caused by interference with the physiologic function of the kidney (e.g. NSAIDs reduce blood flow through the kidney). This is sometimes called **functional renal impairment** because the physical structure of the kidney is not damaged.

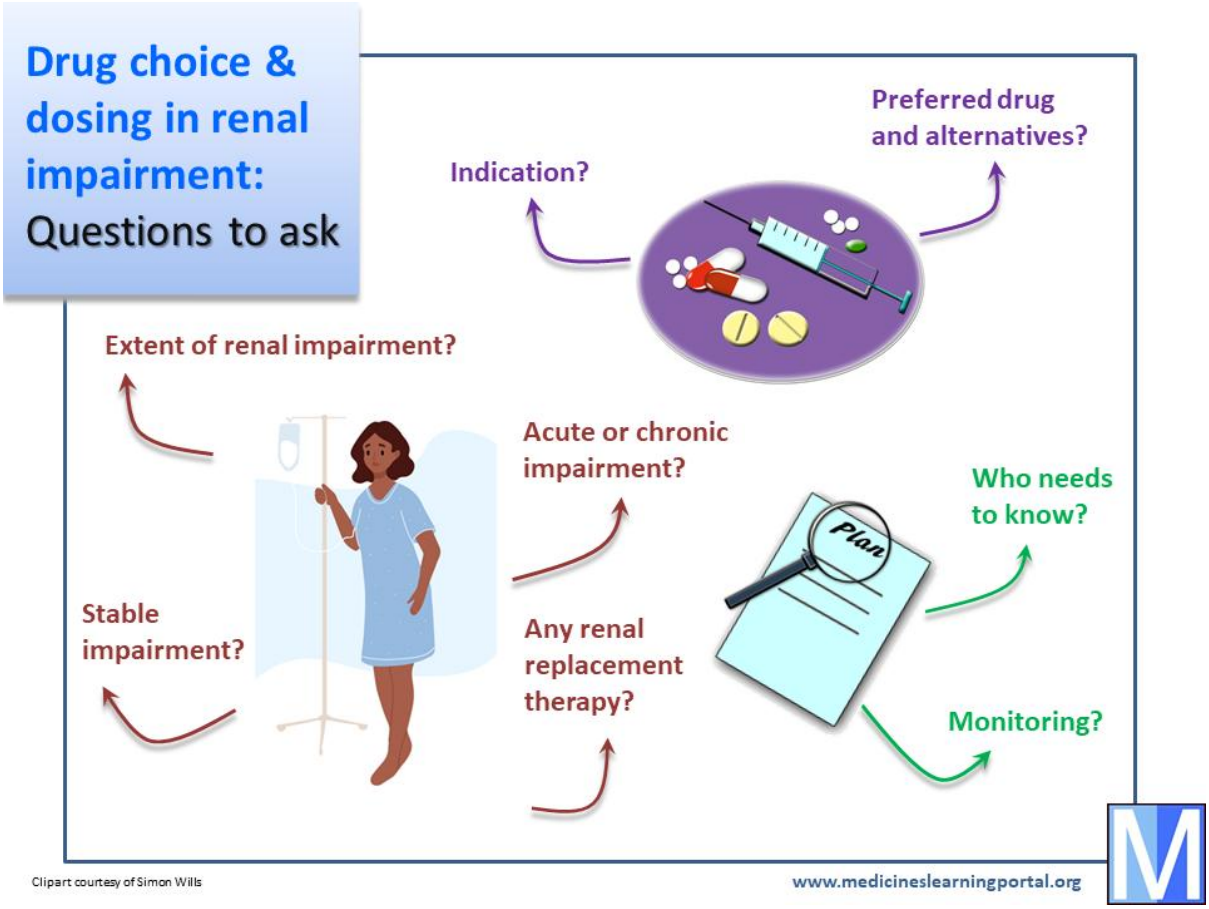
- Physical injury to parts of the kidney (e.g. necrosis of tubules with aminoglycosides). Traditionally, medicines that damage the nephron have been termed **nephrotoxic**.

- Immune-based inflammatory reaction within the kidney presenting as **glomerulonephritis** (e.g. penicillins, gold salts).

Now archived but still useful, NHS England's Think Kidneys programme includes guidelines for medicines optimisation in patients with acute kidney injury (AKI). This gives advice on managing patients with AKI that may be drug-induced and on medicines that may be harmful in AKI. From this document, medication identified as being especially likely to cause AKI include **C**ontrast media, **A**CE inhibitors, **N**SAIDs, **D**iuretics and **A**ngiotensin receptor blockers.

Drugs that are potentially harmful to the kidney should preferably be avoided in any patients with renal impairment as their renal reserve is less and any ill effects may lead to AKI. In end-stage renal failure, where patients are permanently on dialysis and GFR is typically less than 5mL/min, renal function cannot get any worse, so the use of nephrotoxic drugs is acceptable if clinically indicated.

Suggested questions



These specific questions may not apply to every situation you come across, but they are a good starting point for solving clinical problems about prescribing in patients with renal impairment. They are in addition to our general questions to ask in any clinical situation.

The medicine

- What is the indication for the drug? *In case you have to offer safer alternatives. It also helps you to weigh up the potential benefit(s) of using the drug versus the potential risk(s).*
- Which agent would you prefer to use, and are there any alternatives you'd consider? *This helps you focus on therapeutic alternatives that the prescriber thinks are most appropriate to the patient's clinical condition or history.*

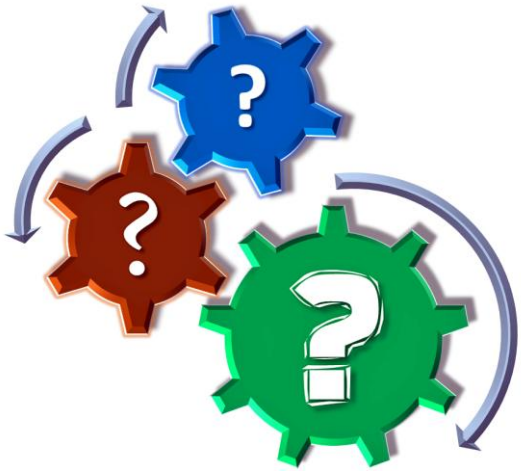
The patient

- Extent of renal impairment? *Calculate the creatinine clearance where necessary, for which you'd need to ask about the age, weight, sex and height of the patient and their serum creatinine.*

- Is this acute or chronic impairment? *Or is it 'acute on chronic' – someone with pre-existing chronic renal failure, who has had a sudden drop in function? An acute impairment might require ongoing monitoring and revision of the dose when the impairment starts to improve.*
- Is renal function stable? *Or is it deteriorating, improving, or fluctuating? This determines whether a dose adjustment that you recommend might need to be revised regularly as renal function changes. A medicine that is largely cleared by non-renal routes is preferable in this situation if possible.*
- Which, if any, renal replacement therapy is being used? *You need to tailor your dose recommendation to the individual patient's circumstances. Ask about the timing of any intermittent peritoneal dialysis or haemodialysis because doses may need to be given post-dialysis.*

Going forward

- Who needs to know? *Who can change therapy or dose if necessary? Is the patient under a specialist renal team? Will the patient and their GP be informed if dose adjustments will affect care after leaving hospital?*
- Who will be monitoring the patient? *If renal function changes, it may affect side effects or efficacy.*



The 'questions to ask' from every tutorial on this site have been brought together into a Quick Question Guide that you may want to download for future reference.

Information sources

If you have a **renal or critical care pharmacist** in your Trust, then ask them for advice about managing any patient where you are not sure.

For straightforward questions about dose adjustment in renal disease, start with the SmPC and then the Renal Drug Database. Both of these sources tend to give practical advice on dosing according to the extent of impairment.

Now archived but still useful, the website Think Kidneys is a helpful NHS resource with videos, information leaflets, and other resources for patients and professionals. In the Resources section there are a suite of tools and educational materials aimed at pharmacists. A particularly valuable tool is the Medicines Optimisation Toolkit for Acute Kidney Injury (AKI) which helps you choose and review medicines in these patients.

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Martindale (or **Micromedex** or **UpToDate** if you have them) can be helpful before you consider undertaking an **Embase** or **Medline** search.

NICE have published several guidelines on managing patients with kidney disease including CKD, RRT and AKI.

Think about whether there may be **expert guidance about the medical condition** you have been asked about from a Royal College or other specialist body/hospital. Sometimes their advice will include options for selected groups of patients such as those with renal disease. The TRIP database may help to you track down any expert guidance quickly.

The SPS website has some guidance on managing enquiries about medicines in patients with renal impairment.

For enquiries about **drug-induced renal failure**, don't forget all your ADR resources.

Be careful about conducting a general internet search on this subject. If you do, you may like to look at our brief guide to evaluating websites about medicines.

Presenting your answer

Once you've asked sufficient questions, gathered the information required and assessed it, you'll need to provide an answer. As a reminder, we offer some general guidance on answering clinical problems. You might like to refresh your memory if you've not looked at this recently.

Next steps in learning…

Your education as a professional never stops, but here are some suggestions to take you beyond what's on this site.

If you have an interest in caring for patients with renal disease, then you should consider joining the UK Renal Pharmacy Group. It's an opportunity to network with colleagues with similar interests, share expert resources, receive training, and keep up-to-date.

Most of the RPG website is only accessible to members, but the site provides free beginners lectures on chronic kidney disease, acute kidney injury and pharmacokinetics and drug dosing in renal impairment. It also has as some brief leaflets on these topics as well as one on caring for a patient with a kidney transplant and one on haemodialysis.

CPPE has a range of learning available on its renal gateway page including an introduction to renal therapeutics, hospital and community case studies, and a quiz.

The Kidn-e Project is a collaboration between the Renal Association, the Royal College of Physicians, and e-LfH. Interactive case-based modules cover the causes, assessment, diagnosis and management of Acute Kidney Injury and Chronic Kidney Disease.

[Last updated: 08 September 2026]