Advanced Clinical Pharmacy – Research, Development and Practical Applications 1

Rhiannon Braund *Editor*

Renal Medicine and Clinical Pharmacy

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Advanced Clinical Pharmacy - Research, Development and Practical Applications

Volume 1

Series Editor
Rhiannon Braund, University of Otago, Dunedin, New Zealand

This exciting new book series *Advanced Clinical Pharmacy* incorporates new areas of research and development with practical approaches and is designed to aid pharmacists up-skill in various new and traditional areas of practice that are applicable, but not limited to, hospital-based care, as well as incorporating the more advanced aspects of community-based care.

Advanced Clinical Pharmacy will incorporate titles that help intermediate level pharmacists see what further areas of practice need to be incorporated in to their skill set, as well as provide guidance on areas of expertise that they may wish to focus on for more advanced practice in the future. It will also provide more advanced pharmacists with a tool for ensuring they are current and up-to-date in a wider range of topics, as well as in their chosen area of expertise. Additionally, it may provide newly registered pharmacists with guidance on what areas of practice they may aspire to work in.

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Titles in the series can be monographs (up to 3 authors) or edited volumes, ranging from 200–500 pages per volume. Each title will be published as ebook as well as in hard bound print format.

This series will be of interest to a wide readership, ranging from intermediate level pharmacists, with experience of 3 to 5 years post-registration (for a bachelor's degree) or experience of 2 to 3 years (for a PharmD), through to more advanced/senior clinical pharmacists. It is hoped that the information would also be of interest to pharmacists working in community-based care, who wish to increase their knowledge and skill, as well as hospital-based pharmacists.

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Unique features

- Offers readers the ability to select the topics that are of interest to them and focus on their area of work/expertise
- Provides the salient points of the background theory but then quickly moves on to more advanced knowledge that contains both current research as well as practical information in the context of cases (but not limited to case scenarios)

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Rhiannon Braund
Editor

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Editor
Rhiannon Braund
University of Otago
Dunedin, New Zealand

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To Emily May White (2002–2017), who gave the gift of life.

Preface

While many young pharmacists emerge into practice with a substantive knowledge base, the evolution of clinical practice coupled with the required additional specialized knowledge that comes from clinical specialties can make it difficult to evolve as a practitioner. This knowledge can be hard to gather from senior clinicians and from specialized medical texts and usually requires a pharmacist to have worked in the specialty for a considerable period of time. These texts facilitate the uptake of this knowledge, by providing the background details of key concepts, in an easy to understand manner and in a way that is targeted specifically to pharmacists.

This series of books have been designed to allow new practitioners, or those moving into new clinical areas, a refresher of the core pharmaceutical concepts, as well as moving on to the rationale optimisation of pharmacotherapy, and finishing with advanced clinical practice. Included are pearls of wisdom, from other practitioners, as well as common pitfalls. This provides a solid platform to then develop further expertise.

In these books, international experts with specialist clinical knowledge have distilled the core knowledge of each clinical area, providing real-world insights to create a book that will help guide junior pharmacists to become the specialist pharmacists of the future.

Dunedin, New Zealand — Rhiannon Braund

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Chapter 1
Introduction to Renal Pharmacy

Carolyn Coulter

Abstract Renal dysfunction is a common reason for requiring pharmacists to adjust their thinking when optimizing a drug dosing regimen. However, many pharmacists find this clinical task quite daunting as there are many factors to consider, such as whether renal clearance alone is affected, if renal metabolism is also affected, if there renal pathology to consider, if this an acute situation or more chronic or even both, and if renal replacement therapy indicated. But if each question is considered in a logical stepwise manner, then often this process becomes much easier to understand. There may still be unanswered questions at the end of this process, but usually there is a great clarity around these and whether they are going to impact the patient clinically.

Keywords Renal pharmacy · Renal dysfunction · Pharmacotherapy · Clinical practice · Nephrology · Pharmacy practice · Adverse drug reactions

Renal dysfunction is a common reason for requiring pharmacists to adjust their thinking when optimizing a drug dosing regimen. However, many pharmacists find this clinical task quite daunting as there are many factors to consider, such as whether renal clearance alone is affected, if renal metabolism is also affected, if there renal pathology to consider, if this an acute situation or more chronic or even both, and if renal replacement therapy indicated. But if each question is considered in a logical stepwise manner, then often this process becomes much easier to understand. There may still be unanswered questions at the end of this process, but usually there is a great clarity around these and whether they are going to impact the patient clinically.

Today there is a greater focus on medicines reconciliation for all patients admitted to hospital, and with this comes the perceived need to prescribe all medicines on

C. Coulter (✉)
Timaru Hospital Pharmacy, Timaru, New Zealand
e-mail: ccoulter@scdhb.health.nz

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admission. However, the very key steps in treating patients with renal dysfunction are to initially ask what may have caused, or contributed to, the renal problem and what may further exacerbate it. Then it is appropriate to ask what medicines are required now, and what medicines will be required in the future. Treating patients with renal dysfunction starts by ceasing or with-holding all inappropriate medicines, followed by the rational prescribing of medicines while always considering the clinical appropriateness, the optimized dosing regimen, and also the pill burden.

For example if you have a patient with an acute kidney injury and you want to review their medicines on admission you firstly need to consider what caused, or contributed, the acute kidney injury. Secondly, what of the regular medicines are currently required, and what can be safely with-held until the kidney injury has resolved. Thirdly, are there any other therapies that should be instigated both for the acute situation and long term for this patient. Chronic kidney disease requires the same analysis, but with a greater focus on the long term requirements.

Initially hospital pharmacists may often consider that dose adjustment as per standard renal dosing guidelines is appropriate, these often do not consider the clinical complexity that may exist. Guidelines for dose adjustments in renal impairment that are based on reduction in glomerular filtration rate, calculated from creatinine clearance, are an excellent staring point, but then critical thinking must be employed.

It is very appropriate to dose adjust a medicine for a chronic condition, but if your patient has severe sepsis then dose adjustment of antibiotics based on creatinine calculations during an acute kidney injury most likely will lead to treatment failure. Instead if the pharmacist considers the pharmacokinetics, the clinical indication including the need to treat aggressively, then a more appropriate dosing regimen may be initiated. This dosing regimen may require frequent review with multiple changes over time, especially if the patient improves – or deteriorates further and requires acute renal replacement. Dose adjustments can also seem complex but these just require consideration of what is the target concentration – is a loading dose required, and for the maintenance dose what proportion is cleared by the kidneys and by how much this will be affected. Additionally, a pharmacist must watch for therapeutic failure as well as potential toxicity.

An appreciation of renal disorders is required for pharmacists who wish to be a valued member of a nephrology team. The kidneys are important for drug dosing as they are one of the most important clearance systems in the body, but they can be affected by processes occurring before the kidneys, such as blood volume and cardiac output, or process after the kidney such as bladder and urological issues. However, there are also many diseases that affect the kidneys – these may be diseases just affecting the kidneys such as glomerular nephritis, or they may be systemic diseases that also result in renal pathology such as systemic lupus erythematosus. The kidneys can also be affected by xenobiotics in the body, which does include other nephrotoxic medicines.

Moreover, the kidneys have a role in acid-base control, electrolyte and water control, they perform some metabolism, as well as regulation of some hormones, and they help control blood pressure. The kidneys can also be affected by congenital structural abnormalities, as well infections, and dysfunction from other organs. If

the kidneys cannot work appropriately then toxins accumulate and can cause other changes in the body. Kidneys are also exquisitely sensitive to oxygen, in part due to the countercurrent exchange needed for electrolyte concentration, meaning they are affected quickly in severe illness or other settings of hypoxia – much more so than say the liver. Kidneys are also unusual in that agents, often when present in high concentrations, can crystalise in the nephrons affecting function. They also handle protein excretion, which can be particularly important to albumin. They are often greatly affected by systematic diseases, for example poor diabetic control with high sugar levels leads to microvascular changes, resulting in great damage and loss of function. Sometimes dysfunction in the kidney is the way a systemic disease is diagnosed, this often occurs when diagnosing multiple myeloma, where a kidney injury may be caused by direct toxicity to tubular cells from the antibodies, from physical obstruction to the kidney, from hypercalcaemia and/or hyperuricaemia, and even from over-use of non-steroidal anti-inflammatories taken for the associated pain.

Renal function is also affected by dysfunction in other organs such as in liver disease when the very serious hepatorenal syndrome occurs, and in heart failure where cardio-renal syndrome may occur. Here, although appropriate dose adjustments may be needed, the most important factor is to treat the organ causing the renal dysfunction. So in heart failure, with associated acute kidney injury, a greater amount of furosemide is usually required, rather than with-holding the diuretic – though an accurate assessment of fluid status must first be done to confirm the patient is volume overloaded.

Pharmacists usually perform therapeutic drug monitoring in their day to day activities, often this is of antibiotics, such as gentamicin or vancomycin. The same principles apply in renal disease, but great care must be taken prevent further renal toxicity. An accurate understanding of the pharmacokinetics processes allows these activities to be done more accurately and with greater confidence.

Patients with renal disease are also much more inclined to develop adverse drug reactions, in part due to changed pharmacokinetics but also due to changed pharmacodynamics and other idiosyncratic processes. It is important as a pharmacist to not just ask what drug does the patient need to be receiving, but also which drug could have caused this harm. Knowledge on adverse drug reactions develops slowly over time but can be enhanced by understanding the underlying principles and knowing what clinical signs to be alert to.

Renal medicine also includes dialysis, and there are many different dialysis modalities available. These may cause confusion when junior staff are consider dosing regimens, but a logical stepwise analysis of these often makes analysis of appropriate dosing regimens easier to understand. There are more published guidelines than ever before, and usually these vary with the different dialysis modalities available. So it is easier to find a range of dosing regimens, but it may be trickier to decide what is appropriate, particularly if you are unfamiliar with the differences between haemodialysis and high-flux haemodialysis, the differences between haemofiltration and haemodiafiltration, and between continuous dialysis and intermittent dialysis (or even quasi-continuous dialysis as some intensive care units run).

One must not overlook the need for specialist pharmacy input for patients who have received a renal transplant – whether that transplant is from a living donor or from a cadaveric donor. Obviously there can be a greater degree of preparation when there is a living donor, but both scenarios lead to many medicines being needed acutely to prevent rejection and keep in check whatever disease first resulted in kidney failure. Opportunistic infections also must be considered, and appropriate agents started. The need for ongoing support and input is crucial, where therapeutic drug monitoring is also critical, and the pharmacist's input is invaluable.

Lastly, long term changes also need to be considered as renal patients are living much longer than previously due to enhances in dialysis and in transplantation. Complications need to be minimized by instigating the most appropriate dosing regimens possible.

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Chapter 2
How Kidney Function Affects Drug Pharmacokinetics

Carolyn Coulter

Abstract The kidney is the most important organ for excreting drugs, including drugs metabolised by the liver, and impaired renal function can influence drug therapy whether that dysfunction is acute kidney injury (AKI), chronic kidney disease (CKD), or both (AKI on CKD). Pharmacokinetics (PK) underpins drug dosing, and kidney dysfunction can impact on absorption, distribution, metabolism, and elimination (ADME). Drug effects, that is pharmacodynamics (PD), may also be altered. Additionally, existing clinical conditions may also worsen, and adverse drug reactions (ADRs) are both more common and more severe in renal disease.

Keywords Renal · Pharmacokinetics · Acute kidney injury · Absorption · Distribution · Metabolism · Elimination · Renal clearance · Cockcroft & Gault equation · Drug dosing · Renal impairment · Chronic kidney disease

The kidney is the most important organ for excreting drugs, including drugs metabolised by the liver, and impaired renal function can influence drug therapy whether that dysfunction is acute kidney injury (AKI), chronic kidney disease (CKD), or both (AKI on CKD). Pharmacokinetics (PK) underpins drug dosing, and kidney dysfunction can impact on absorption, distribution, metabolism, and elimination (ADME). Drug effects, that is pharmacodynamics (PD), may also be altered. Additionally, existing clinical conditions may also worsen, and adverse drug reactions (ADRs) are both more common and more severe in renal disease.

It is important to fully understand PK to ensure the most appropriate dosing regimen for the clinical situation is implemented to maximise patient outcomes. While PK is broadly categorised as absorption, distribution, metabolism, and elimination, this is not necessarily a linear process. After absorption elimination can occur while

C. Coulter (✉)
Timaru Hospital Pharmacy, Timaru, New Zealand
e-mail: ccoulter@scdhb.health.nz

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distribution and metabolism are also occurring. In addition, while renal dysfunction can greatly affect elimination, whether of the parent drug or the metabolite(s), it can also have more minor effects on absorption, distribution, and metabolism.

The kidney is a complex organ; anatomically it has an outer zone called the cortex and an inner medulla, where these dictate its function. The nephron is the functional unit, and there is around one million nephrons in each kidney. The glomerulus of each nephron starts in the cortex, which is followed by the proximal tubule, then the loop of Henle, and the distal tubule which goes to the collecting duct. Cortical nephrons have a short loop of Henle that remain in the cortex, while juxamedullary nephrons have extended loops into the medulla and have greater water reabsorbing and urine concentrating ability.

2.1 Absorption

Absorption most frequently means oral absorption from orally administered drugs, but it can also mean absorption via transdermal, rectal, subcutaneous, intramuscular, buccal, intranasal or other routes, where each route is affected by different factors. Oral administration can be affected by gastric stasis and gastroparesis in renal disease, most likely from uraemia, delaying delivery to the small intestine. However gastric 'dumping' may also occur; this is when food, and other agents like medicines, move very quickly from the stomach to the duodenum, which can facilitate rapid delivery and absorption in the small intestine. The net effects these processes have on drug absorption depends on where the drug is usually absorbed and whether the agent is being used acutely or chronically. For example if a gastric motility agent like metoclopramide is administered to reduce nausea and overcome gastric stasis, then this can decrease gastrointestinal transit time and decrease the time of onset of a drug e.g. paracetamol. However, increased motility may also decrease absorption of some drugs e.g. digoxin absorption, which occurs in the proximal small intestine and may be reduced with metoclopramide.

Absorption is also affected by food; usually this is the rate of absorption rather than the extent, unless chelation is involved. The extent of absorption is reflected in the bioavailability (F) or more accurately the oral availability. While the rate of absorption is reflected in the time to the maximum plasma concentration (t_{max}). With acute dosing t_{max} is important, such as onset time with analgesics, but with chronic dosing t_{max} is less important. Food intake may also be decreased from nausea and vomiting due to uraemia in renal disease. If a drug is absorbed in the stomach, a high fat meal will reduced gastric emptying and increase the extent of absorption, this was historically used to increase the amount of griseofulvin absorbed before the newer antifungals were available.

Acidity can also be affected in renal diasease, pH is usually around 2 but may be increased to closer to 4 decreasing acid hydrolysis and increasing the amount of drug absorbed. Acidic drugs are largely unionised and absorbed in the stomach, however drugs like insulin and benzylpenicillin are degraded at low pH, so a higher gastric pH

value may give less degradation. Drugs such as antacids, histamine-2 receptor antagonists, and protein pump inhibitors may increase gastric pH, affecting absorption of other drugs. Additionally, the small intestine has a much higher pH of approximately 8 and a very large surface area, so for the many drugs absorbed here, increasing gastric emptying will give faster onset and may possibly reduce acid degradation.

Medications used in chronic renal disease (CKD) can include phosphate binders, as phosphate is difficult to remove by dialysis so binding reduces the amount absorbed, such as calcium carbonate or aluminium hydroxide. These drugs are similar to antacids and calcium while effectively binding phosphate can also chelate other drugs like the fluoroquinolones ciprofloxacin and moxifloxacin. This results in less drug absorbed risking therapeutic failure. The dosing regimen may also impact the degree of chelation, and spacing these medicines two hours apart may avoid this problem. However complicated regimens can impact compliance and compliance with phosphate binders is often low as is complying with a low phosphate diet. Additionally, there is the risk of pharmacobezoars forming which can cause serious complications. The newer chelator sevelamer may also alter absorption of other medicines by chelation, for example furosemide.

Absorption may depend on lipid solubility – which can affect uptake across cell membranes into cells. Absorption can be related to dose, for example the absorption of gabapentin is saturable, so as the dose increases the percent absorbed reduces (and this is why it is difficult to acutely overdose on gabapentin). Oedema of the gastrointestinal tract also makes the gut much less efficient at absorbing drugs, and this particularly becomes problematic when there is heart failure coexisting with renal failure.

Controlled release products also affect absorption, and this is used to extend the apparent half-life – where what has happened is the absorption becomes the rate limiting step in the elimination. Often in renal impairment slow release preparations are not needed as the reduced clearance means the drug has a greatly extended half-life, and controlled release preparations may just increase the risk of accumulation.

F is defined as the ratio between the area under the concentration–time curve (AUC) for the oral (PO) formulation and the intravenous (IV) formulation:

$$F = AUC_{PO} / AUC_{IV}$$

However it is important to note that overall changes in absorption and bioavailability are generally of limited clinical significance. After absorption drugs then get taken into the portal circulation and move on to the liver, where first pass metabolism may be affected.

Note patients on continuous peritoneal dialysis (CAPD) can administer drugs by the peritoneal route by adding the drug to the peritoneal dialysis fluid, and this is particularly useful for delivering antibiotics during episodes of peritonitis. Intraperitoneal administration gives excellent absorption when the membrane is inflamed during infection; additionally the site of absorption is also the site of action. The intraperitoneal route works well for administering drugs such as gentamicin, vancomycin, and cephalosporins, in peritonitis.

2.2 Distribution

The volume of distribution (Vd) is the proportionality constant relating the amount (A), or dose (D), in the body to the plasma concentration (Cp):

$$A = Cp \times Vd$$

$$Vd = A / Cp$$

Or

$$Vd = D/Cp$$

The volume of distribution is how much plasma you would need, for the total amount of the drug to be present at the current plasma concentration, if the drug was confined to the plasma/blood compartment. Physiologically it also reflects how much is bound to tissues and is not present in the blood; it does not reflect true distribution.

If Vd is approximately equal to the blood volume then all the drug is present in the blood and virtually none is present in the tissues, for example heparin which is highly protein bound and remains in the circulation has a Vd of around 0.07 L/kg. If Vd is larger, then the drug may be water soluble and distributed throughout the body water, such as lithium with a Vd of ~0.7 L/kg, but if Vd is very large then very little is present in body water and most of the drug is actually bound to the tissues, for example digoxin with a Vd of ~7L/kg.

Distribution is also affected by metabolites, urea, and other toxins accumulating and crossing membranes, and the changing permeability of these membranes, as well as concentration gradients and osmotic pressure. Oedema and fluid overload are common in renal dysfunction, whether CKD or AKI, due to the difficulty excreting water, which can increase Vd. However water soluble drugs with low protein binding may have a reduction in their effective Vd. Tissue binding may also be affected, where metabolic waste products may displace drugs, e.g. digoxin bound to tissues can be displaced by urea. Blood flow can also affect Vd, generally by affecting the rate of presentation to tissues, for drugs that are highly tissue bound and have a large Vd.

Many drugs bind to plasma proteins, where acidic drugs generally bind to albumin and basic drugs to α_1-acid glycoprotein. Protein binding can also occur with lipoproteins. Protein binding is saturable, and there is usually the fraction of drug that is unbound (fu) in equilibrium with the fraction bound, and it is the unbound fraction that elicits the biological response.

$$\text{Free drug} + \text{free protein} \leftrightarrow \text{drug} - \text{protein complex}$$

Albumin is often greatly decreased in renal disease, especially CKD where it may have decreased slowly over a long period of time. Decreased albumin results in a greater fraction of a drug being unbound, but there is also a compensatory increase in clearance, meaning the net effect is only a small change in the fraction unbound

with little clinical significance. Organic acids may accumulate in renal failure, and compete for drug binding with albumin and other plasma proteins, but again this does not usually result in a clinically significant interaction. Rarely do changes in protein binding mean there should be a change in loading dose, nor a change in steady-state drug concentrations, however phenytoin is an important exception to this, where concentrations should be corrected for low albumin unless 'free' (i.e. unbound) phenytoin concentrations are measured.

Oedematous disorders in renal failure, particularly nephrotic syndrome, leads to retention of water and sodium, and this can increase Vd via 'third spacing' where the extracellular fluid space is expanded. Administering albumin will not result in an increase in albumin concentration, rather it is used as a colloid fluid replacement, increasing the blood volume rather than administering crystalloid fluid which leaks into the extracellular fluid and the interstitium.

Acidic drugs generally bind to albumin, e.g. cefazolin, ceftriaxone, doxycycline, furosemide, ibuprofen, methotrexate, metolazone, phenobarbital, phenytoin, salicylate, sulfamethoxazole, thiazides, valproate, and warfarin, and may have increased fu in renal disease. Basic drugs e.g. amphotericin B, chloramphenicol, chlorpromazine, diazepam, fluoxetine, ketoconazole, propranolol, quinidine, and tricyclic antidepressants, bind to α_1-acid glycoprotein which is generally unchanged.

Vd may be increased due to a combination of reduced protein binding, increased tissue binding, and fluid overload e.g. cefazolin, cefuroxime, erythromycin, furosemide, gentamicin, phenytoin, trimethoprim, and vancomycin may have an increased Vd in renal dysfunction. However other drugs show a reduction in Vd with renal disease e.g. chloramphenicol, digoxin, and ethambutol. Note changes in protein binding that occur in CKD are not correct by dialysis renal replacement, but they are corrected by kidney transplantation.

It is important to consider where fluid goes during volume replacement, and this depends on the type of fluid administered. The crystalloid sodium chloride 0.9% goes to extracellular fluid and only about 20% remains in plasma where the rest becomes interstitial fluid – often worsening oedema. Dextrose 5% is electrolyte free and goes to total body water as glucose is taken up by cells, so only around 12.5% goes to plasma and red cells. Colloids such as albumin result in most of the fluid being retained in the plasma, as the oncotic effect of the colloid holds the fluid inside the capillary endothelial barrier, making them useful in fluid replacement.

2.3 Metabolism

Biotransformation largely occurs in the liver, but it is not limited to this one organ and the kidney is also a site of biotransformation. Overall, hepatic metabolism may be decreased in low glomerular filtration rate (GFR); mechanisms are unclear but may include urea and other toxins in the plasma acting to inhibit liver enzymes – this process is normalised to some degree by dialysis. This means there may be accumulation of both active and inactive metabolites. The effect of renal disease on

individual hepatic reactions may however be varied. There may be increased or decreased oxidation, while glucuronidation is usually unchanged, but hydrolytic reactions are often slowed as is reduction. Metabolism may also be reduced in other organs, and there are changes in uptake and efflux pumps such as P-glycoprotein. As expected CKD has a much larger effect on metabolism than AKI, where the exact causes are unclear but may include uraemia, increased inflammatory state, and oxidative stress. Additionally, there is still large interindividual variability with metabolism which can be partially linked to sex, age, and weight.

The kidney has also has the ability to biotransform drugs by cytochrome (CYP) P450 enzymes, including 1A2, 2C9, 2C19, 2D6, and 3A4; plus via N-acetyl transferase, glutathione transferase, and renal peptidase. The kidney actually has similar levels, based on weight, of these enzymes to the liver, however as it is smaller in size its overall capacity is less than that of the liver. Agents biotransformed in the liver include vitamin D, where its activation is decreased in CKD. So renal osteodystropthy is difficult to treat as colecalciferol cannot be metabolised by the kidney to the active 1-α hydroxylated product; so calcitriol (1-α, 25-dihydroxycolecalciferol) or alfacalcidol (1-α hydroxycolecalciferol) should be used. Hydroxylation of steroids and arachidonic acids also occurs in the kidney, as well as gluconeogenesis. The degradation of insulin occurs in the kidney, so the effect of insulin is prolonged in CKD and also often in AKI. Additionally other drugs and xenobiotics may be biotransformed in this organ.

Low molecular weight (MW) proteins may be filtered in the glomerulus but not found in urine, this is because they are metabolised by enzymes in the brush border of the lumen of the proximal tubule. While high MW proteins, e.g. albumin, are transported into the proximal tubular cells by endocytes and metabolised by lysosomal enzymes. Generally catabolism continues until amino acids are formed, which are then reabsorbed into the vasculature. The antibiotic imipenem is also hydrolysed by renal brush border enzymes, in this case by dihydropeptidases which are decreased in renal impairment. So “non-renal” drug clearance does actually occur in the kidney.

Many drugs are metabolised in the liver and then the metabolites excreted by the kidney, but in CKD if the metabolites are active the duration of effect may be greatly increased. For example morphine is metabolised to morphine 6-glucuronide, which is much more potent than the parent drug, and then this accumulates in CKD, hence fentanyl (with inactive metabolites and a short half-life) is often the opioid of choice for end stage renal disease (ESRD). If the metabolites are inactive, but cause toxic adverse effects, these may be enhanced in renal disease - for example with meperidine (pethidine) normeperidine increases resulting in a greater risk of seizures.

2.4 Elimination

Excretion of drugs and metabolites usually occurs in the urine but a small amount is excreted in the faeces plus very small amounts in sweat, tears, bile, and via the lungs and skin. The kidneys are roughly 0.5% of body weight, but receive 20–25% of

cardiac output, that is around 1200 mL/min. Around 10–20% is filtered in the glomerulus where glomerular filtration rate (GFR) is approximately 125 mL/min, while the other 80–90% becomes luminal fluid. Note filtration occurs due to hydrostatic pressure, where the ultrafiltrate contains electrolytes and small solutes. Nearly all, 99%, is reabsorbed and this is mostly water and sodium (which is affected by diuretics), leaving the amount of urine formed being 1–2 mL/min, or about ~1.5 L/day. Along with this approximately 25–30% of drugs are excreted unchanged in the urine.

Clearance (CL) of a drug is a proportionality constant relating rate of elimination (RE) to the plasma concentration (Cp):

$$RE = CL \times Cp$$

$$CL = F \times D / AUC$$

Most drugs have first order kinetics (but a few drugs have saturable or zero order kinetics) so concentration decreases as time increases, and a constant fraction is eliminated, which gives the half-life, that is the time for the serum concentration to drop by 50%.

The rate constant (k) is defined as:

$$k = CL / Vd$$

$$t_{1/2} = \ln 2 / k = 0.693 / k = 0.693\,Vd / CL$$

Clearance is made up of hepatic clearance (CL_H), that is metabolism, as well as renal clearance (CL_R) and clearance by other routes (CL_{other}) e.g. skin, lung:

$$CL = CL_R + CL_H + CL_{OTHER}$$

The kidney is made up of many nephrons each made up of the glomerulus, the proximal tubule, the loop of Henle, the distal tubule, and the collecting duct tubules; there are also the afferent and efferent vessels. Physiologically clearance is determined by blood flow to the kidney, the ability to filter at the glomerulus, and then any secretion in the proximal tubule as well as reabsorption in the distal tubule. Drugs must be polar, that is water soluble, to be removed by the kidneys or they must be metabolised to more polar compounds to then be removed. Filtration is favoured by low molecular weight (MW) (<500 Da) and less protein bound substances, and it occurs under positive hydrostatic pressures through pores of 7–8 nm in the glomerular membrane. Approximately 20% of water soluble, low molecular weight compounds, that are non-protein bound in plasma enter the filtrate and this includes drugs. Drug transport in the kidney can be via passive diffusion, carrier mediated or facilitated diffusion, active transport, or endocytosis/pinocytosis.

Renal excretion of a drug:

$$CL_R = \text{filtration} + \text{secretion} - \text{reabsorption}$$

Secretion occurs via active, that is energy dependent, processes involving organic anion transporters (OATs) or organic cation transporters (OCTs) on both the basolateral and apical membranes, and continues from capillaries of the blood stream to the proximal renal tubules. Organic acids secreted include cephalosporins and penicillins, furosemide, probenecid, salicylates, sulphonamides, and thiazides. While organic bases secreted include amiloride, amantadine, cimetidine, dopamine, morphine, pethidine, and tetracyclines. Multi-drug resistance proteins also secrete drugs, like P-glycoprotein on the renal proximal tubule which acts as an efflux pump removing drugs e.g. digoxin. Substances can compete for OATs or OCTs, as these transporters have saturable kinetics, and relative substrate specificity may become important leading to drug-drug interactions, e.g. probenecid and penicillin, or drug-endogenous substances, e.g. cotrimoxazole causing an increase in serum creatinine (which is not related to a decline in GFR but only due to competition for secretion transporters). Secretion allows clearance to exceed GFR up to renal blood flow of 1200 mL/min. It lowers the concentration of unbound drug, then further drug dissociates from protein complexes, allowing more drug to then be transported, so even highly protein bound drugs may be cleared almost completely from the blood by a single pass through the kidney, for example penicillin is rapidly cleared in one pass. Morphine is transported by OCTs while its metabolites the glucuronide and sulfate conjugates are excreted by glomerular filtration and OATs. While secretion is saturable only a small part of renal clearance is secretion so this means secretion saturation is not normally clinically relevant, except in drug-drug interactions when more than one drug competes for these transporters.

The loop of Henle runs a countercurrent exchange system to allow the urine to become maximally concentrated and maximal water to be reabsorbed, otherwise a large amount of very dilute urine would be produced (which is what happens when a severe AKI is resolving). Tubular reabsorption is via passive diffusion, so there is no carrier system to become saturated, which occurs predominantly in the distal tubules but also in the proximal tubule, loop of Henle, and collecting duct. It depends on the concentration gradient, lipid solubility, pH, and favours uncharged molecules passing through the lipid membrane. Reabsorption includes water, carbohydrates, amino acids, vitamins, and drugs - especially if lipid soluble. Only polar and the least diffusible compounds stay in the urine. Ion trapping or pH partitioning can occur, as the pH of urine is 5–6 while the pH of blood is 7.4, so the pH can also be manipulated changing reabsorption. There is also some active reabsorption in the nephron, for example lithium is actively reabsorbed in the tubule.

As water is reabsorbed the tubular fluid becomes more concentrated creating urine and helping drugs diffuse from the distal tubular fluid back to the blood stream. Overall this reduces renal clearance, otherwise if a drug was neither secreted nor reabsorbed it would end up approximately a hundred times more concentrated in urine than unbound in plasma. Only unbound and unionised drug, that is lipid soluble drug, can move through the tubular cells during reabsorption because reabsorption, unlike secretion, requires diffusion through a lipid membrane, hence lipid soluble drugs are not efficiently excreted in urine. Osmotic diuretics like mannitol,

which is filtered but not reabsorbed, so does not have site specific action in the kidney, also alter the concentration gradient so less drug is reabsorbed as less water is reabsorbed and there is a lower concentration gradient causing greater renal clearance. These processes all act on the fraction unbound (fu) which is also what elicits the therapeutic effect and this may be reduced in renal failure. Additionally, in renal disease each nephron is thought to either be fully functional or non-functional, this is the intact nephron hypothesis.

For a drug that is filtered, secreted and/or reabsorbed:

$$CL_R = fu\left(GFR + CL_S\right) \times \left(1 - FR\right)$$

$$CL_S = \text{secretion}$$

$$FR = \text{fraction reabsorbed}$$

If a drug is only filtered, or filtered plus secreted and reabsorbed at the same rate then:

$$CL_{Drug} = fu \times GFR$$

If a drug is more secreted than reabsorbed:

$$CL_{Drug} > fu \times GFR$$

If a drug is more reabsorbed than secreted:

$$CL_{Drug} < fu \times GFR$$

With reabsorption it is important to realise renal clearance varies with urine flow. Dilute urine is formed when urine flow is high, as there is less reabsorbed filtered water so solutes have a lower concentration gradient and less drug is reabsorbed. As only unbound drug diffuses across membranes, equilibrium is reached when the concentration of the unbound drug is equal to the concentration of the unbound drug in plasma, but from a kinetic perspective this may not be achieved.

Ion trapping can occur depending on the urine pH and the pKa of the drug. Urine pH is typically 4.5–7.5, but unlike plasma it is not well buffered, so nonpolar weak acids with pKa values between 3 and 7 such as aspirin, salicylates, and phenobarbital are pH sensitive. For example at pH 4.5 aspirin is unionised and reabsorbed in the renal tubular lumen, but at pH 7.5 aspirin is ionised and not able to be reabsorbed so there is greater excretion. Thus in aspirin overdose excretion can be enhanced by manipulation of the pH by alkaline diuresis. However if the pKa of the drug is very low, say below 2 as is the case for chromoglycic acid, the drug is completely ionised at all urine pH values so it cannot be manipulated, however clearance is high at all pH values. For acids with a high pKa, such as phenytoin where it is above 8, the drug is mostly unionised so clearance is low and again insensitive to pH changes. Alkaline diuresis can be used to remove weakly acidic drugs in poisoning, however

potassium must be monitored as it is hard to alkalinise urine if the patient has hypokalaemia, however care must be taken to not use acetazolamide to raise the pH as this causes systemic acidosis and will increase the toxicity of salicylates.

Weakly basic non-poplar drugs with pKa values between 6 and 12, such as amphetamine, are reabsorbed in alkaline urine, but have increased excretion in acidic urine so urine acidification with ammonium chloride (NH_4Cl) will increase their removal. If they are a very weakly basic non-polar drug with a pKa of less than 6, such as propoxyphene, they are extensively reabsorbed at all urine pH values because there is sufficient drug in the diffusible non-ionised form at all times to enable reabsorption. For strongly basic drugs with a pKa above 12, like guanethidine, there is little reabsorption at all urine pH values because ionisation is extensive so clearance is high and independent of pH. Additionally, basic drugs that are polar in their unionised form are not reabsorbed, regardless of degree of ionisation in urine (unless actively transported), and clearance is independent of pH, a good example of this is gentamicin. However, most weak acids and weakly basic drugs are cleared mainly by the hepatic route so pH manipulation is of little clinical significance except when treating overdoses.

Forced diuresis, such as with mannitol, will increase urine output and also increase the excretion of drugs that are usually extensively reabsorbed. If reabsorption is also pH sensitive altering this may also increase clearance. So if forced diuresis greatly reduces reabsorption, for example from 85% to 15% then changing the pH is not needed as so little is being reabsorbed, but if forced diuresis only partly reduces reabsorption, say from 85% to 50%, then manipulating the pH may affect the 50% that is reabsorbed.

GFR is heavily influenced by arteriolar tone upstream (afferent) and downstream (efferent) from the glomerulus. Agents that affect vascular tone will then affect GFR, for example the renal prostaglandin PGE_2 will increase glomerular filtration and sodium excretion. Non-steroidal anti-inflammatory drugs (NSAIDs) will inhibit prostaglandins, including PGE_2 and lead to a reduction in GFR. While this is not usually a problem, it will becomes problematic if on lithium therapy as there will be less lithium excretion and potential toxicity. Note angiotensin-converting enzyme inhibitors give an almost diagnostic doubling of serum creatinine if administered to a patient with renal artery stenosis due to the effect on the vasculature. The immunosuppressant ciclosporin is also nephrotoxic because it causes intrarenal vasoconstriction reducing GFR, as well there can be acute changes to the proximal tubules and ischaemic nephropathy.

Renal calculi, that is kidney stones, can alter elimination and may be caused by changes in pH, low citrate levels, and infections – especially if ammonia is released by bacteria. Calcium oxalate forms spikulated stones during hyperoxaluria and hyperuricosuria, calcium phosphate stones form from high pH and renal tubular acidosis, while uric acid forms lamellar stones during low pH and hyperuricosuria, and struvite ($MgNH_4PO_4$) stones form from urease producing bacteria increasing the pH and causing cystinuria. If the stone fills the renal pelvis it is called a ‘staghorn’ calculus and will give a cast of the calyces and renal pelvis. While it is com-

mon to think decreasing calcium may reduce stone formation paradoxically it may actually increase stone formation as less oxalate is bound in gut so there is greater oxalate absorbed and more potential to form calcium oxalate stones while oxalate is being excreted in the urine.

Serum creatinine (SCr) is measured and used to calculate creatinine clearance (CrCl) in order to estimate GFR. Serum creatinine is easy and fast to measure but it is not ideal. Some creatinine is secreted, so using CrCl to estimate GFR will provide an overestimate in cases of very poor renal function as secretion is relatively preserved compared to filtration. Creatinine is from muscle breakdown so it varies with sex, age, and weight/muscle mass. It is important to watch for situations where muscle mass is low as renal function appears better than it actually is, for example in immobile patients, patients with spinal cord injuries, and the elderly. Also, if protein has been ingested creatinine may be falsely elevated so renal function is under estimated. Ideally the perfect compound for measuring GFR would be freely filtered with minimal protein binding, and neither be secreted nor reabsorbed, plus not be metabolised, toxic, or change the filtration rate, plus easily measured in plasma and urine. Inulin and sinistrin are freely filtered and not protein bound so they can be a good marker of GFR but they are exogenous polysaccharides which limits their usefulness. Para-aminohippuric acid is actively secreted in one pass through the kidney, so filtered and secreted but not reabsorbed, so it can be used to give a measure of renal blood flow or to study the anion transport system but again it is exogenous.

GFR can be estimated in adults by calculating the CrCl using the Cockcroft and Gault equation, from the measured SCr, but if CrCl is only 10% of normal the GFR will be overestimated by a factor of two so the resulting CrCl should be halved. There are also other equations for calculating CrCl, while laboratories often report estimated GFR (eGFR) as it only requires SCr, age, and sex, but it is per 1.73 m^2 so it does then need to be corrected for size. However, these are only accurate for serum creatinine values that are at steady state, that is stable, so should not be used in AKI.

Cockcroft and Gault equation:

$$\mathrm{CrCl}\left(\mathrm{mL/min}\right) = 1.23\left(\mathrm{or}\,1.04\right) \times \left(\left(140 - \mathrm{age}\right) \times \mathrm{IBW}\right) / \mathrm{SCr}\left(\mathrm{micromole/L}\right)$$

Use 1.23 for males and 1.04 for females.

Ideal body weight (IBW) is usually used rather than actual body weight (ABW), but in obesity consider using adjusted body weight (adjBW):

$$\mathrm{adjBW} = \mathrm{IBW} + 0.4\left(\mathrm{ABW} - \mathrm{IBW}\right)$$

Creatinine clearance can also be more accurately obtained by measuring urinary creatinine (UCr) and volume of urine (V):

$$\mathrm{CrCl}\left(\mathrm{mL/min}\right) = \mathrm{UCr} \times \mathrm{V}\left(\mathrm{mL}\right) / \mathrm{SCr} \times \mathrm{time}\left(\mathrm{min}\right)$$

2.5 Catergorisation of Chronic Kidney Disease

CKD is usually categorised into five classes depending on eGFR, where class 1 and 2 also require the presence of protein in the urine, and class 5 is end stage renal disease (ESRD) which also includes pre-dialysis.

CKD 1	Normal eGFR ≥90 mL/min per 1.73 m^2 plus proteinuria
CKD 2	Mildly decreased eGFR 60–89 mL/min per 1.73 m^2 plus proteinuria
CKD 3	Moderately decreased eGFR 30–59 mL/min per 1.73 m^2
CKD 4	Severely decreased eGFR 15–29 mL/min per 1.73 m^2
CKD 5	ESRD eGFR <15 mL/min per 1.73 m^2

2.6 Drug Dosing in Renal Impairment

Drug dosing in renal impairment is not necessarily well represented by using the classes of mild, moderate, and severe impairment despite many references providing dosing guidance this way; however these are quick and easy to use. The intact nephron hypothesis is the concept that each nephron is either non-functioning or fully functioning, so renal disease is the net result of a reduced number of fully functioning nephrons, so the fraction of drug cleared unchanged by the kidney is reduced by the degree of renal impairment, and dose reductions are usually proportional to the degree of renal impairment.

Proportional dosing:

$$\mathrm{D}\left(\text{renal impairment}\right) = \mathrm{D}\left(\text{normal}\right) \times \mathrm{CL_{CR}} / \mathrm{CL_{CR}}\left(\text{normal}\right)$$

Or calculate the proportional dose needed from the fraction excreted unchanged (FU):

$$\mathrm{D}\left(\text{renal impairment}\right) = \left(1 - \mathrm{FU}\right) + \mathrm{FU} \times \mathrm{CL_{CR}}\,\mathrm{pt} / \mathrm{CL_{CR}}\left(\text{normal}\right)$$

If the drug is completely metabolised then FU is equal to zero and a dose reduction is not required. If FU is 0.5 then only 50% is excreted by the kidneys, so if there was a 50% reduction in renal clearance the dose should be reduced by 50% of 50% which is 25%.

Additionally, while references give advice from studies and PK calculations about dosing in CKD very little advice is given, or known, for AKI, so it is important to consider the pharmacokinetics carefully.

But drug dosing is not ‘one size fits all’ and consideration of the whole regimen is important. In sepsis full dosing for 24–48 (or even 72) hours of antimicrobials is often appropriate, to ‘fill up Vd’ as under-dosing is as problematic as overdosing,

and third spacing into extracellular spaces may well be occurring due to dysfunction of biological barriers. Another example is paracetamol where 1 g TDS may be more appropriate giving better analgesia, due to a higher peak, than 750 mg QID, even though the total amount given is the same.

Drugs that have a wide therapeutic range, and predominantly metabolised (less than 30–40% is excreted unchanged) are often dosed as in normal renal function where precise dose changes are not usually required. But drugs that are largely cleared by the kidneys, have a narrow therapeutic range, plus a high protein binding (where organic acids displace the drug in renal failure), or a small volume of distribution (so changes in fluid affect the drug) do require dose adjustment as per renal function, which may require decreased dose and/or decreased frequency. Remember if an inactive metabolite is cleared by the kidneys, it may also cause problems if toxic. Assumptions often include that the desired plasma or tissue concentration is the same in renal disease as in normal renal function, but this may not be so. For example with digoxin high potassium changes target concentrations, plus (unmeasured) active metabolites may also increase affecting response. Additionally other PK parameters may be altered, in third spacing tissue fluid has a pH of around 7 while plasma has a pH of 7.4 so ion trapping into the more acidic tissues can occur.

The loading dose (LD) is proportional to Vd (which is little affected by renal impairment) and the target concentration, or concentration at steady state (Css), while the maintenance dose (MD) is proportional to the CL – which may be greatly affected by renal impairment.

$$\mathrm{LD} = \mathrm{Vd} \times \mathrm{Css}$$

$$\mathrm{MD} = \mathrm{CL} \times \mathrm{Css}$$

Vd and CL are independent parameters, while clearance affects half-life which can guide dosing interval. Note the plasma concentration is used as a proxy for the concentration at the receptors, but receptor binding affinity will also determine the effect – including how long the effect lasts (tightly bound drugs have slower dissociation). Therapeutic action should be considered, e.g. gentamicin bacterial killing is related to peak concentrations, so the same dose (or slightly reduced) used less frequently will be as effective, whereas for penicillins killing is related to time above the minimum inhibitory concentration (MIC) where the dose is usually decreased and frequency is less affected (though a continuous infusion may give the best killing).

Therapeutic drug monitoring (TDM) can be used to guide dosing, where plasma concentrations are more closely related to the drug effect than the dose. TDM is useful when inter-individual PK variability exists, if the therapeutic effect (or adverse drug effect) is correlated to the drug concentration, where there is a defined target concentration, if there is a narrow therapeutic range, and/or the therapeutic effect itself is difficult to monitor. TDM can also help detect errors – overdoses and under-doses, which is important to know as this would alter subsequent dosing e.g. with-holding nephrotoxic medicines, or initiating earlier re-dosing. However it is

important to remember the target tissue is the site of action which is not normally the plasma so also treat the patient clinically and not just the number.

$$\text{Dose} \rightarrow \text{Plasma concentration} \rightarrow \text{Drug effect}$$

TDM may require plasma trough concentrations if close to steady-state, peak concentrations if these are related to activity, or several concentrations if calculating the AUC. Generally it is assumed there is linear PK over the therapeutic range. TDM is also very helpful for drugs greatly affected by renal impairment, for example vancomycin and gentamicin which unlike many antibiotics do not have a wide therapeutic range. These are cleared by renal elimination - filtered only, not protein bound, so clearance is proportional to creatinine clearance. Gentamicin is an aminoglycoside, effective against Gram negative infections, but nephrotoxic and ototoxic. It is not metabolised but cleared by the kidneys, and has a small Vd, so dosing is based on ideal body weight (IBW), and peak concentrations predict toxicity to microbes, that is effectiveness. AUC is linked to nephrotoxicity, while ototoxicity is more complex. In renal impairment extending the interval, say to every 36–48 h, rather than a large dose reduction, will give the best killing. Also gentamicin has a post-antibiotic effect (PAE) which ensures killing continues once levels drop.

Vancomycin is a glycopeptide that is cleared by the kidneys but it also has a larger Vd (0.4 L/kg), so dosing is often based on actual body weight (or if obese an adjusted body weight), also around 50% is bound to plasma proteins. Killing is based on the time the microbe is exposed to the antibiotic, so the concentrations should not drop too low. It is usually given several times a day, with a loading dose, and trough concentrations are monitored once steady state is achieved, however in severe renal impairment dosing is greatly reduced.

Additionally, consider whether the drug can reach the site of action, this is particularly important with diuretics. Loop diuretics need to get to the loop of Henle but in low GFR this is difficult, so much higher doses may need to be used. For example furosemide is incompletely and erratically absorbed from the gut, then highly protein bound (so little is presented to glomerulus), after filtration the drug is then actively secreted into the proximal tubular lumen via OAT which increases its concentration to have the desired physiological effect; but in renal failure it is less effective as there is a much lower GFR and more organic acids to compete for tubular secretion, so higher doses are required.

Consider also drug interactions, in patients with suspected meningitis they may be receiving high dose aciclovir as well as high dose ceftriaxone. Aciclovir can crystalise in the kidneys, due to insufficient fluid, then an AKI results, leading to accumulation of the ceftriaxone, which can give penicillin induced encephalopathy, which is very difficult to distinguish from the original meningitis.

The ideal drug to use in renal impairment is metabolised but has no active metabolites or toxic metabolites, has a disposition that is unaffected by fluid shifts or changes in protein binding, has a response which is unaffected by altered tissue sensitivity, has a wide therapeutic range, and is not nephrotoxic.

2.7 Ageing and Renal Impairment

Ageing impacts renal clearance, where there is a drop in renal blood flow and GFR drops by about 1% (or around 1 mL/min) per year after the age of 30 years. There is debate whether this decline is due to pathological, that is due to comorbidities, or physiological processes, but elderly do have fewer functioning nephrons. Age related changes in renal function also include decreased renal mass, especially corticol mass, reduced tubular function including secretion (affects penicillins), concentrating ability (resulting in nocturnal polyuria), diluting capacity, drug excretion, sodium handling, potassium handling, acid-load excretion, fluid handling, erythropoietin production, renin and aldosterone levels, plus increases in atrial natriuretic peptide, and antidiuretic hormone (vasopressin). CKD 3 is present in approximately 70% of people over 70 years due to vascular disease and renal ageing, and there are also more renal tract diseases from infections, and for men from prostate disease. In the unstressed state sufficient renal clearance usually remains for removal of waste, regulation of volume, and other homeostatic mechanisms, but under stress, e.g. dehydration or sepsis, renal function often becomes insufficient – resulting in AKI.

Age results in reduction in hepatic clearance also, and Vd may change due to a reduction in lean body mass and an increase in fat content, along with a reduction in body water. Loading doses of water soluble drugs, which have a smaller Vd, so doses may be based on IBW. However, loading doses of fat soluble drugs, which may have an increased Vd, should be based on total body weight. Half-life becomes prolonged, so time to steady state is also prolonged, and with slower elimination dose intervals may need to be longer to prevent drugs accumulating. Additionally, due to the reduction in muscle mass, creatinine levels may be falsely low, disguising the true reduction in renal clearance. Plus there may be polypharmacy creating multiple drug-drug interactions.

2.8 Dialysis

Dialysis is the main form of renal replacement therapy (RRT) but there is also kidney transplantation, either from a live donor or a cadaveric donor. Indications for dialysis include hyperkalaemia especially if causing cardiac instability, persistent fluid overload, acidosis, uraemia causing encephalopathy, pericarditis, bleeding, anaemia, anorexia, and/or nausea and vomiting. RRT removes toxins but also beneficial drugs like antibiotics. Pharmacokinetics are altered in dialysis, where the situation of virtually nil elimination of substrates including drugs and toxins alternates with some elimination. The degree of removal depends on the characteristics of the drug and the dialysis prescription.

There are different types of dialysis; haemodialysis (HD), performed intermittently, involves drugs and toxins flowing passively across a semipermeable membrane down a concentration gradient into a dialysate (electrolyte and buffer)

solution, again using a counter current flow to maximise toxin removal. Drug removal is greater if MW <600 Da, there is low protein binding, and the drug is water soluble with a small Vd e.g. salicylates, methanol/ethanol, lithium, and theophylline – else the drug may stay in the tissues and not be delivered to the dialysis membrane. Clearance also depends on the dialysis prescription – membrane type and filter surface area, and blood and dialysate surface flow rates. Membranes are porous rather than biological lipioidal barriers, so clearance is not related to ionisation or lipophilicity, and efficiency is measured by the extraction coefficient.

High flux dialysis it a type of HD which more closely mimics the human kidney, it involves using a dialyser membrane with a larger pore size and a higher ultrafiltration coefficient, plus increased blood and dialysate flow rates. This results in a greater clearance of low MW solutes e.g. urea, as well as more middle and high MW (<20,000 Da) agents being cleared e.g. vancomycin (MW = 1449 Da) which is not normally removed by HD but drops by about 20% with high flux HD.

Knowing clearance helps to determine appropriate dosage regimens, where clearance in the dialysis machine depends on the product of the extraction ratio and the blood flow rate, which is calculated from the amount of drug recovered unchanged in dialysate (R) and the area under the pre-dialyser plasma concentration-time curve during the period dialysate was collected:

$$CL_{Total} = CL_{Residual} + CL_{Dialysis}$$

$$CL_{Dialysis} = R / AUC_{0\text{-}t}$$

The half-life of a drug is also reflected by the residual clearance and the dialysis clearance, note if the patient is anuric there is nil residual clearance.

$$t_{1/2} \text{ off HD} = 0.693 \text{ Vd} / CL_{Residual}$$

$$t_{1/2} \text{ on HD} = 0.693 \text{ Vd} / \left(CL_{Residual} + CL_{Dialysis}\right)$$

There are several forms of continuous dialysis such as haemofiltration, haemodialysis, and haemodiafiltration. Haemofiltration has low clearance but done continuously is effective, and it has less volume changes than HD so can be used acutely in unstable patients. Filtration uses a hydrostatic pressure gradient to drive fluid through a semipermeable membrane. Small solutes (MW <10,000 Da) pass through the membrane with the fluid, i.e. solvent drag. Filtration can remove a lot of fluid but less toxins. Drug clearance is a function of membrane permeability (the sieving coefficient) and the rate of ultrafiltration formation which can be increased by increasing pressure. Continuous haemodialysis removes solutes by diffusion across a semipermeable membrane, where water removal is passive and follows solute removal. Haemodiafiltration, gives a combination of ‘dialysis’ plus ‘filteration’.

Haemoperfusion, not strictly dialysis, involves the passage of blood through a bed of activated charcoal or other such material like polystyrene beads, this removes agents like theophylline, phenobarbitone, and carbamazepine. Drug size, water sol-

ubility, and protein binding are less important as there is direct contact so it removes more nonpolar organic molecules.

Peritoneal dialysis has a poor extraction ratio and slow flow rate giving low clearance, but may be performed continuously (CAPD) to overcome this. Clearance is determined by a drug's size, solubility, degree of ionisation, protein binding, and Vd. Additionally, intrinsic properties of the peritoneal membrane affect clearance e.g. blood flow, and peritoneal membrane surface area (~1–2 m^2) and permeability (to compounds MW <30,000).

Renal transplants give very good clearance after successful transplantation, better than dialysis, but the kidney never works perfectly. Generally 50% of nephrons are functioning, but the clearance is also affected by immunosuppressants, as these may be inherently nephrotoxic.

2.9 Drug Dosing in Dialysis

Drug clearance during dialysis is related to filter membrane composition, ultrafiltration rate, blood flow rate, and dialysate flow rate. It is important to consider if the drug is dialyzable (and to what extent), not dialysed, or has unknown dialysability. Generally drugs removed by dialysis (or filtration) are water soluble, have a low MW and low Vd, but a high fraction unbound, and are usually cleared by the kidneys. Drugs that are removed by dialysis may need to be dosed post-dialysis, but not dosed between sessions, and considerable variations in published regimens may exist. Dialysis alters fluid and electrolytes, which may change the response to a drug. It is important to watch for drug redistribution after dialysis as rebound increases in plasma concentrations may occur, e.g. lithium rebounds due to slow diffusion from cells in tissues (note distribution in the tissues also limits the amount of lithium dialysis can physically remove), digoxin is another drug that also rebounds post-dialysis, and gentamicin concentrations may increase 25% within one to two hours of HD. Drugs altering blood flow may even potentially alter dialysis e.g. vasodilators/constrictors.

Dialysis is also used in toxicity, for example in overdose. Methanol and ethylene glycol overdoses are treated with ethanol or fomepizole, but this intentionally blocks their metabolism (so the toxic metabolites of methanal/formaldehyde and oxalic acid are not formed), so the agent then must be removed with dialysis as removal via the skin and lungs is very slow. In drug overdoses concentration dependent kinetics arise, so assessment of dialysability is more difficult than at therapeutic concentrations.

Note elimination may be continuous during dialysis, such as with CAPD and continuous dialysis; while IHD gives a situation of 'on' and 'off' clearance. Note clearance via dialysis is much lower than even moderately impaired RF. Residual renal clearance may also be important; patients who are not anuric produce about 100 mL of urine per 24 h. Remember with a transplanted kidney, the kidney only has about 50% usual function, and there is only one. So while the function may be fine, drugs may still require dose adjustment.

2.10 Pharmacokinetics and Pharmacodynamics

Pharmacokinetics (PK) is the effect the body has on the drug, whereas pharmacodynamics (PD) is the effect the drug has on the body. PD effects may be changed in renal failure, such as increased sensitivity to opiates and benzodiazepines possibly due to increased meningeal permeability. Other examples are increased effects to antihypertensives, possibly due to autonomic dysfunction and increased bleeding with uraemia due to decreased platelet function (desmopressin may be used to reduce bleeding). Drug therapy can also further exacerbate and worsen renal failure, due to PK and PD effects; nephrotoxins like NSAIDs should be avoided as these cause increased fluid retention, drugs that worsen uraemia like tetracyclines (minocycline but not doxycycline) via antianabolic effects are problematic, and drugs that decrease blood flow such as nitrates may give hypotension. As well adverse drug effects are usually more problematic in these patients due to both PK and PD changes.

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Chapter 3
Acute Kidney Injury: Pre-renal, Intra-renal and Post-renal

Christine Sluman, Pooja Mehta Gudka, and Kathryn McCormick

Abstract Acute kidney injury (AKI) occurs when there is an acute fall in glomerular filtration rate (GFR) resulting in a reduction of kidney function.

The causes of AKI can be categorised as:

- **Pre-renal,** generally in which decreased renal blood flow results in a drop in GFR
- **Intrinsic/intra-renal,** in which a disease process causes damage to the kidney itself
- **Post-renal,** in which a process downstream of the kidney prevents drainage of urine (urinary tract obstruction)

These categories are discussed in more detail below. The classification and treatment of AKI is discussed elsewhere.

Keywords Acute Kidney Injury · Pre-renal · Post-renal · Intra-renal · Kidney – anatomy · Kidney – physiology · Glomerular filtration · Medication mechanism

Learning Points:

- Categorisation of acute kidney injury into pre-renal, intra-renal and post-renal, their causes and early management
- Basic anatomy and physiology of the kidney and urinary tract

C. Sluman (✉)
North Bristol NHS Trust, Bristol, UK
e-mail: christine.sluman@nbt.nhs.uk

P. M. Gudka
Royal Free London NHS Foundation Trust, London, UK
e-mail: poojamehta.gudka@nhs.net

K. McCormick
NHS Greater Glasgow and Clyde, Glasgow, UK
e-mail: Kathryn.McCormick@ggc.scot.nhs.uk

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- Renal blood flow and compensatory mechanisms to preserve glomerular filtration pressure
- Mechanisms of how different classes of medications can cause acute kidney injury

3.1 Pre-renal AKI

Pre-renal AKI is the most common type of AKI and occurs when a sudden reduction in blood flow to the kidneys (reduced renal perfusion) results in ischaemia and a loss of kidney function. The injury is often reversible on prompt restoration of renal perfusion, however if the ischaemia is prolonged or severe this can result in tissue death in the kidneys (acute tubular necrosis or ATN) and lead to permanent damage.

Pre-renal AKI can be a complication of almost any disease, condition, or medicine that causes a decrease in the amount of blood or fluid in the body, and is the most common cause of AKI in both the community and hospital settings.

3.1.1 Anatomy and Physiology of the Kidney

In order to understand the pathophysiology of pre-renal AKI, it is first necessary to understand the processes that regulate blood flow to the kidney, maintain glomerular filtration pressure, and control the amount of fluid reabsorbed by the kidney.

The nephron is the main functional unit of the kidney, and consists of a glomerulus and a tubule which leads to a collecting duct. The glomerulus comprises a ball of capillaries surrounded by the Bowman's capsule. Urine is formed by hydrostatic filtration of blood in the glomerular capillaries. Blood that is about to be filtered enters the capillaries of the glomeruli through afferent arterioles and leaves though efferent arterioles. A high glomerular capillary (hydrostatic) pressure is necessary for filtration to occur; as glomerular capillary pressure drops so does the GFR. The filtrate enters the Bowman's capsule and is then modified in the tubules by reabsorption, secretion and excretion of water, electrolytes, and other substances such as glucose and amino acids.

Glomerular filtration pressure can be maintained either by vasodilation of afferent arterioles (increasing blood inflow) primarily mediated by prostaglandins, or vasoconstriction of efferent arterioles (restricting blood outflow) primarily mediated by angiotensin II (see Fig. 3.1).

The renin-angiotensin-aldosterone system (RAAS) plays a central role in the regulation of renal blood flow. When renal perfusion is reduced, the kidneys secrete renin which mediates the cleavage of angiotensinogen to angiotensin I. Next, angiotensin-converting enzyme (ACE) cleaves angiotensin I to produce angiotensin II. Angiotensin II is a potent vasoconstrictor and acts peripherally to increase arteriolar vasoconstriction, thereby increasing blood pressure. Within the kidneys angiotensin II vasoconstricts the glomerular arterioles, but has a greater effect on efferent arterioles than afferent, resulting in increased glomerular filtration pressure.

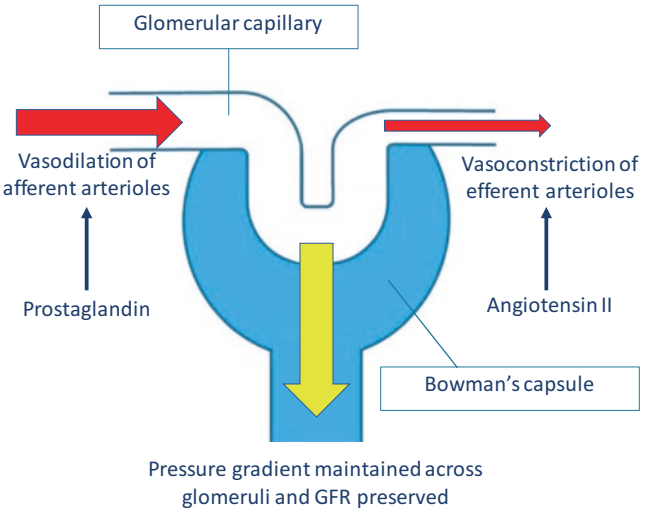

Fig. 3.1 Normal compensatory response to reduction in renal blood flow

This differential effect on the efferent and afferent arterioles may be due to a number of reasons. The efferent arteriole has a smaller diameter than that of the afferent arteriole. Angiotensin II also stimulates the release of the vasodilator nitric oxide from the afferent arteriole, and therefore the constrictive effect is minimised.

Angiotensin II also stimulates secretion of the hormone aldosterone from the adrenal cortex. Aldosterone promotes reabsorption of sodium and water from the renal tubules into the blood, thereby increasing circulating blood volume, blood pressure and renal perfusion.

Finally, angiotensin II stimulates the release of antidiuretic hormone (ADH, or vasopressin) from the hypothalamus. Vasopressin also exhibits vasoconstrictive properties; however, its main effect is to stimulate water reabsorption in the collecting ducts thereby increasing circulating blood volume (See Fig. 3.2).

There are a number of other complex mechanisms by which renal blood flow can be autoregulated, including sympathetic nervous system mediated efferent arteriolar constriction (through release of renin and subsequent actions as described above), and the action of vasodilatory prostaglandins.

3.1.2 Causes of Pre-renal AKI

Pre-renal AKI results either from a generalised reduction in systemic tissue perfusion and associated reduction in renal perfusion, or a selective reduction in renal blood flow.

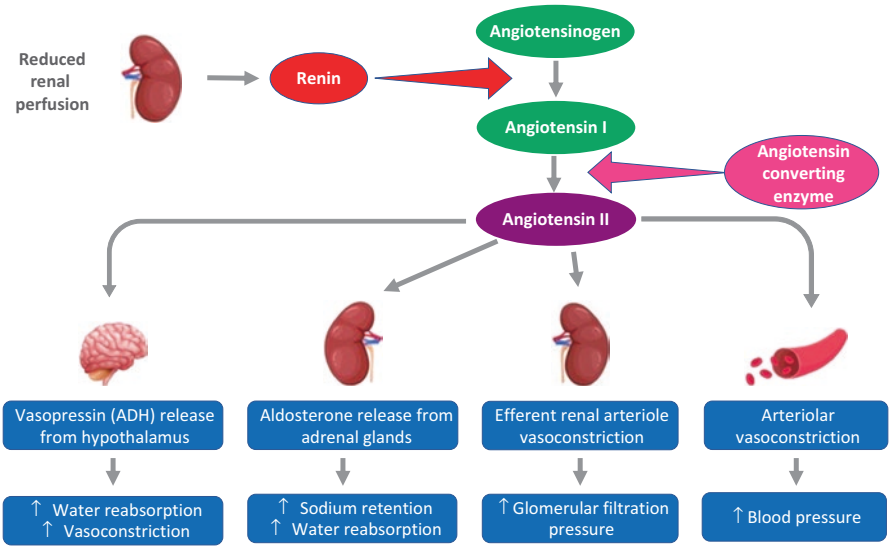

Fig. 3.2 Autoregulation of renal blood flow (organ images obtained from Adobe Stock. Used with permission)

- **Reduction in systemic tissue perfusion**

  A fall in systemic tissue perfusion can result from:

(i) reduced circulating blood volume
(ii) reduced cardiac output (e.g. cardiac failure), or
(iii) systemic vasodilatation (e.g. septic shock)

This is detected by baroreceptors in the heart and arteries. Stimulation of these receptors results in increased sympathetic nervous system activity and release of renin (with resultant production of angiotensin II) and vasopressin. These actions lead to an increase in cardiac output, arteriolar and venous vasoconstriction, and salt and water retention, resulting in an increase in tissue perfusion. Arteriolar vasoconstriction occurs predominantly in the renal, splanchnic (internal organs) and musculoskeletal vasculature in an attempt to maintain blood flow to the heart and brain.

During mild to moderate reductions in cardiac output or intravascular volume, the predominant vasoconstrictive action of angiotensin II on efferent renal arterioles is the main mechanism by which glomerular filtration pressure is preserved. However, if renal perfusion continues to fall, either as a result of falling cardiac output or ongoing systemic vasodilation, further increases in angiotensin II levels results in a more pronounced effect on afferent arteriolar vasoconstriction, leading to a decline in GFR and development of AKI.

(i) Reduced circulating blood volume

A common cause of pre-renal AKI is a reduction in circulating blood volume. This might be due to true volume depletion, either as a result of increased gastrointestinal (GI) losses (vomiting, diarrhoea, GI bleeding), increased renal losses (diuretic use, osmotic diuresis such as in diabetic ketoacidosis), or increased insensible losses (severe burns or pyrexia). It may also be a result of fluid shift out of the intravascular space into the extravascular compartment/tissues as occurs in hypoalbuminaemic states such as nephrotic syndrome, pancreatitis and cirrhosis, and states that cause capillary leak such as sepsis and anaphylaxis. Conditions that reduce circulating blood volume, such as GI bleeding or use of diuretics or paracentesis, may further reduce renal perfusion and precipitate AKI.

(ii) Reduced cardiac output

In cardiac failure, the systemic vasoconstriction and salt and water retention seen as a result of the RAAS activation described above increases cardiac afterload, further reducing cardiac output and renal perfusion. The use of diuretics will often result in an improvement in kidney function as a result of a reduction of cardiac afterload, improvement in cardiac contractility and improved cardiac output.

(iii) Systemic vasodilation

In septic shock, cytokines released as part of the inflammatory response to sepsis cause systemic vasodilation, increased capillary permeability and hypotension.

In advanced liver disease, increased production and activity of vasodilatory substances such as nitric oxide in the splanchnic circulation produces arterial vasodilation. As above, activation of the RAAS system occurs with renal vasoconstriction and salt and water retention.

- **Selective reduction in renal blood flow**

i. Drugs that affect glomerular blood flow.

Drugs that affect glomerular blood flow can reduce the GFR by lowering the hydrostatic pressure that drives the filtration process.

Increased production of angiotensin II in response to reduced renal perfusion stimulates the synthesis of vasodilatory prostaglandins by cyclooxygenase (COX) enzymes in the glomerulus. These prostaglandins produce afferent vasodilation, helping to maintain GFR and minimise ischaemia. Use of non-steroidal anti-inflammatory drugs (NSAIDS) and cyclooxygenase-2 inhibitors (COX2 inhibitors) blocks the production of these prostaglandins, with a resultant reduction in afferent vasodilation and fall in GFR.

Angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARBs) block the vasoconstrictive effect of angiotensin II on efferent arterioles, decreasing the pressure gradient across the glomeruli and cause a drop in GFR.

Calcineurin inhibitors (CNIs) such a ciclosporin and tacrolimus may cause vasoconstriction of the afferent and efferent glomerular arterioles with a resultant fall in glomerular blood flow and GFR.

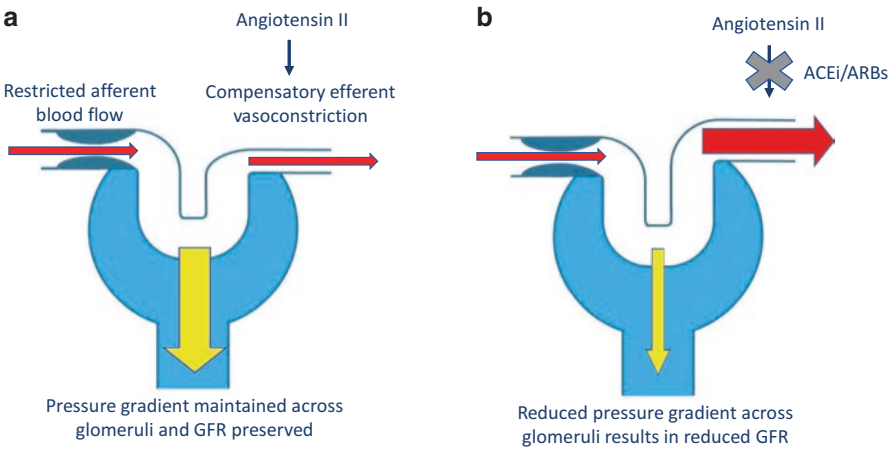

Fig. 3.3 Effect of ACEi/ARBs in renal artery stenosis. (**a**) Normal compensatory response to renal artery stenosis (**b**) Effect of ACEi/ARBs in renal artery stenosis

ii. Renal arterial obstruction

Obstruction of the renal artery can result from:

(a) renal artery thrombosis/embolus
(b) aortic aneurysm
(c) renal artery stenosis

In patients with renal artery stenosis, the ability to increase afferent blood flow by vasodilatation is limited due to the stenosis. The main compensatory mechanism available to preserve GFR is therefore efferent arteriolar vasoconstriction mediated by angiotensin II. Use of ACEi or ARBs which block the action of angiotensin II removes the kidney's only available mechanism to maintain the glomerular filtration pressure in these patients, resulting in a decline in GFR (see Fig. 3.3). Many patients will see some degree of drop in GFR and rise in serum creatinine on starting an ACEi or ARB, however the effect is more profound and serious in patients with bilateral renal artery stenosis, which makes this a contraindication to their use. It important to check baseline serum creatinine (eGFR) and potassium before initiating ACEi or ARBs and repeat approximately 1 week after initiation and each dose increase.

Any combination of the factors described above can further increase the risk of developing AKI, for example volume depletion in a patient on a NSAID. Patients with existing chronic kidney disease may also have an impaired ability to compensate for a fall in renal perfusion and are at increased risk of developing acute on chronic renal failure.

In patients deemed to be at high risk of developing an AKI, provision of 'sick day rules guidance' to temporarily withhold ACEi inhibitors, ARBs, diuretics and NSAIDs during intercurrent illnesses such as diarrhoea, vomiting, fever or infection may be considered (Table 3.1).

Table 3.1 Causes of pre-renal AKI

Aetiology	Pathophysiology and conditions	
Reduction in systemic tissue perfusion	Reduced circulating volume	Increased GI losses (vomiting, diarrhoea)
		Blood loss (GI bleed, trauma)
		Diuretics
		Osmotic diuresis (DKA)
		Increased insensible losses (significant burns)
		Fluid shift out of intravascular space into extravascular compartment (nephrotic syndrome, pancreatitis, cirrhosis, sepsis, anaphylaxis)
	Systemic arterial vasodilatation	Sepsis
	Reduced cardiac output	Cardiac failure
		Acute myocardial infarction
Selective reduction in renal perfusion	Drugs that affect glomerular blood flow.	NSAIDs/COX2 inhibitors – inhibit synthesis of vasodilatory prostaglandins
		ACEi/ARB – block vasoconstrictory effects of angiotensin II
		CNIs – increase vasoconstriction
	Renal arterial obstruction	Renal artery thrombosis/embolus; aortic aneurysm; renal artery stenosis

Abbreviations: *GI* gastrointestinal, *ACEi* angiotensin converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *NSAID* non-steroidal anti-inflammatory drug, *COX2* cyclooxygenase II inhibitor, *CNI* calcineurin inhibitor

3.1.3 Treatment of Pre-renal AKI

The management of pre-renal AKI involves treating the underlying cause and restoring renal perfusion. Depending on the aetiology of the injury this may either involve volume repletion, increasing cardiac output (which may require diuresis) and/or stopping an implicated medication.

In patients presenting with a clinical history of fluid loss (vomiting, diarrhoea, or bleeding) and clinical findings consistent with hypovolemia (tachycardia, decreased skin turgor, hypotension including postural hypotension), administration of intravenous fluids is typically the first step to improving renal perfusion.

The choice of intravenous fluid is influenced by concurrent electrolyte abnormalities, however will generally involve administration of a balanced salt solution such as Hartmann's or Ringer's lactate. The rate and volume of fluid therapy varies with the severity of the hypovolemia, and is governed by blood pressure response and other clinical signs such as peripheral perfusion, mental status, and urine output. Volume status may require monitoring with a central venous pressure (CVP) catheter to avoid over- or under-replacement of fluid.

If hypotension persists despite adequate volume repletion to return the patient to a euvolaemic state, medications to increase blood pressure (vasopressors) and/or improve cardiac output (inotropes) may be required to improve renal perfusion.

Intravenous fluid therapy is generally not indicated in patients with volume overload, for example in cardiac failure, cirrhosis, or in patients with pulmonary oedema. In AKI associated with cardiac failure, treatment options include improving cardiac function with the use of diuretics to reduce volume overload and cardiac afterload, or with the use of inotropes.

In AKI due to a specific condition called hepatorenal syndrome, treatment may involve the administration of vasopressin analogues such as terlipressin to produce splanchnic vasoconstriction and increase systemic vascular resistance.

3.2 Intra-renal AKI

Intra-renal causes of AKI refer to intrinsic damage to the structure of the kidney. The function of the kidney is dependent on its tightly co-ordinated structure. Disruption to any part of this highly inter-dependant architecture can lead to an injury, causing renal failure. Ischaemia is the main cause of AKI, especially intrinsic damage. Ischaemic injuries to the kidney may cause vasoconstriction, endothelial damage and activate an inflammatory process. This leads to an increase in oxygen demand by the tubular cells as well as reduced delivery of oxygen and metabolites through the kidney, causing cellular damage (apoptosis or necrosis) and therefore organ dysfunction.

Intra-renal causes of AKI are a challenging form of injury to evaluate as there are a wide variety of injuries that can occur to the kidney structure. Intra-renal AKI is categorised by the section of the kidney that is primarily affected:

(i) Glomeruli
(ii) Tubules
(iii) Vascular structure
(iv) Interstitium

3.2.1 Glomerular Causes of AKI

The glomerulus receives 25% of cardiac output. Renal pressure and perfusion through the glomerular capillaries affect the filtration rate. The glomerular basement membrane (GBM) acts as a barrier, only allowing passage of molecules depending on their size and charge. Macromolecules such as albumin are unable to be filtered through glomeruli. Specialised cells known as podocytes are present on the urinary side of the GBM which acts as a further filtration barrier.

Table 3.2 Drugs known to cause infra-renal acute kidney injury

Glomerulonephritis:	Tubular necrosis	Interstitial Nephritis
Penicillins	Aciclovir	Allopurinol
	Aminoglycosides	Aminosalicylates
Penicillamine	Amphotericin	Azathioprine
Pamidronate	Cephalosporins	Carbamazepine
Allopurinol	Cisplatin	Cephalosporins
Dapsone	Contrast	Co-trimoxazole
NSAIDs	Ciclosporin	Calcium channel blockers
Gold	Foscarnet	Aminoglycosides
Hydralazine	Loop Diuretics	Isoniazid
Rifampicin	Lithium	Lithium
Thiazide diuretics	NSAIDs	NSAIDs
	Mannitol	Penicillins
	Tacrolimus	Phenytoin
	Vancomycin	Proton pump inhibitors
	Paracetamol	Quinolones
		Rifampicin
		Thiazide diuretics
		Vancomycin

Acute inflammation of blood vessels and glomeruli can result in AKI. Deposition of immune complexes (antibody-antigen complexes, complements and immunoglobulins) especially in the GBM can lead to a reduction in the glomerular filtration rate, increased intravascular volume, salt and water retention and hypertension. These features can be either drug-induced (see Table 3.2) or caused by manifestations of immune mediated systemic illnesses e.g. systemic lupus erythematous (SLE), Goodpastures syndrome, Granulomatosis with polyangiitis. Activated neutrophils and macrophages can also directly injure the glomerulus in diseases such as antineutrophil cytoplasmic antibody (ANCA) associated vasculitis. Extra-capillary accumulation of macrophages fibroblasts and fibrins can lead to damage to the capillary cell walls and rupturing of the glomerular membrane, known as glomerulonephritis (GN). Patients with glomerulonephritis can present with either acute or chronic kidney injury. The main feature suggestive of glomerulonephritis is the presence of blood and significant amounts protein in the urine.

Podocyte dysfunction in diseases such as Minimal Change disease, diabetes mellitus or amyloidosis can lead to protein leaks (proteinuria) through glomeruli. Nephrotic syndrome (defined by high levels of protein in urine, low levels of albumin in blood paired with significant oedema) may not typically present in patients with an acute injury but may lead to an acute on chronic kidney injury in patients with glomerulonephritis.

Management of glomerulonephritis is usually supportive and disease specific. The patient must undergo a kidney biopsy to obtain a definitive diagnosis. Treatment options may include high dose steroids in addition to cytotoxics e.g. cyclophosphamide and/or monoclonal antibodies e.g. rituximab. Plasma exchanges can be used to remove the offending antibodies. Supportive therapies aim to preserve renal function by:

- Reducing proteinuria
- Controlling oedema
- Controlling blood pressure
- Reducing risk of blood clots
- Providing correct adjunct treatment to prevent side effects of agents used to treat GN

3.2.2 Tubular Causes of AKI

Approximately 99% of the glomerular filtrate is reabsorbed from the renal tubules leading to the production and concentration of urine. Tubular epithelial cells have a high metabolic rate and are most vulnerable to ischaemic injury. Changes in glomerular perfusion pressure can lead to ischaemia. Tubular cells can adapt to survive in an ischaemic environment, however any insult that further reduces the already critical supply of metabolites can cause tubular cell injury. Presence of nephrotoxic agents and/or ischaemia can also cause detachment of the cells from the tubular basement membrane and cell death (necrosis). Accumulation of the detached cells can lead to tubular obstruction. These mechanisms lead to a change in reabsorption and a reduction in urine output (see Fig. 3.4). Acute tubular necrosis (ATN) is the most common cause of intra-renal AKI especially in hospitalised patients.

Drugs and chemicals can induce nephrotoxic ATN. Accumulation of drugs or metabolites; high doses or even normal doses of nephrotoxic agents can lead to injury especially in patients who already have high risk factors for developing AKI. Risk factors include age, CKD, hypertension, diabetes, cardiovascular and peripheral vascular disease. ATN can develop after short- or long-term exposure to the offending drug/metabolite. Nephrotoxic agents include drugs e.g. aminoglycosides, cisplatin (see Table 3.2); heavy metals e.g. lead and mercury and solvents e.g. ethylene glycol.

Contrast induced ATN (contrast-nephropathy) is thought to be caused by direct tubular toxicity, oxidative stress, renal ischaemia and vasoconstriction, all leading to reduced renal perfusion. The actual mechanism is not very well defined.

Ischaemic ATN tends to occur in patients who have undergone recent major surgery, trauma or burns, are severely hypovolaemic, or septic. Tumour lysis syndrome after chemotherapy, rhabdomyolysis, hyperthermia, seizures, sepsis can lead also to deposition of haemoglobin, myoglobins and uric acid crystals all of which can cause intratubular obstruction and AKI.

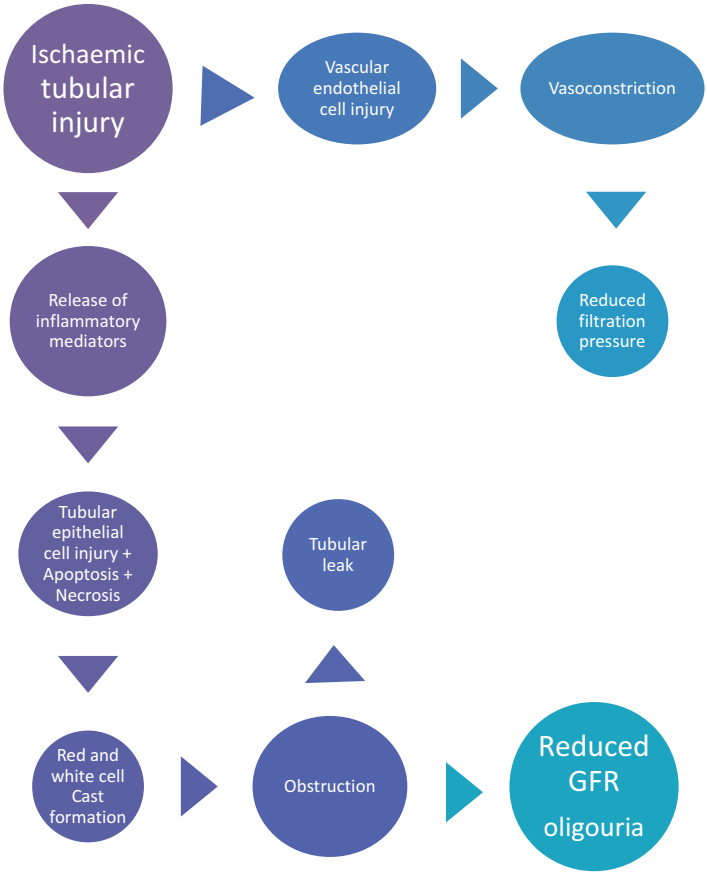

Fig. 3.4 Consequences of Acute Tubular Injury

ATN is associated with high mortality and morbidity rates and takes a long time to improve. It is mostly reversible depending on the extent of the injury and time taken to diagnose and treat. Unlike pre-renal AKI, in ATN, once the injury has occurred recovery takes a long time even with restoration of kidney perfusion. The patient may require renal replacement therapy (RRT) to aid recovery. The duration of time on RRT depends on the extent of the injury and presence of pre-existing CKD. In severe cases damage can be irreversible leaving the patient requiring long-term RRT. Optimal recovery depends on early diagnosis and timely treatment. Recognition and removal of the nephrotoxic agent(s), monitoring urine output, maintaining normal fluid balance and regulating electrolyte concentrations are key to treatment. Patients tend to become polyuric during the recovery phase and therefore may require extra fluid replacement. Maintaining fluid balance is key.

In order to avoid ATN it may be prudent for medical practioners to place surveillance measures especially in patients who are at high risk of developing AKI. These measures include:

- Avoiding nephrotoxic agents where possible
- Ensuring appropriate dosing, timing and frequency of medications
- Timely therapeutic drug monitoring when applicable
- Maintaining adequate hydration
- Routine monitoring of renal function – serum creatinine, urea, electrolytes, albumin, urine protein: creatinine ratios.

3.2.3 Vascular Causes of AKI

Acute events involving renal blood vessels can reduce renal perfusion thus reducing GFR. Both the large and small blood vessels can be affected. Atherosclerotic plaques in renal blood vessels can cause thrombosis. The size of the vessel(s) affected would determine the signs and symptoms at presentation as well as diagnosis. In conditions such as pre-eclampsia, malignant hypertension and haemolytic uraemic syndrome activation of the coagulation cascade, red cell apoptosis and tubular necrosis can lead to endothelial damage of the small blood vessels causing reduction in GFR. Capillary cell wall damage due to vasculitis mainly affects the glomeruli but damage can occur anywhere throughout the nephron further leading to organ dysfunction. Cholesterol emboli in a large vessel could lead to renal vein thrombosis or renal artery stenosis, both of which could lead to irreversible damage if not treated in a timely manner.

A full history, physical examination and imaging would be required to confirm diagnosis. Treatment would include management of the underlying condition e.g. blood pressure management, anticoagulation, stenting, avoidance of offending medications e.g. ACEi / ARBs in renal artery stenosis, addition of secondary prevention medications e.g. statins.

3.2.4 Interstitial Causes of AKI

The kidney interstitium is the space outside the glomeruli and in between the tubules. It also contains specialised cells and interstitial fluid. Disruption to the renal interstitium can also have profound effects on renal function. Acute interstitial nephritis (AIN) is the third most common cause of AKI after pre-renal AKI and acute tubular necrosis. It occurs as a result of infiltration of inflammatory cells e.g. eosinophils in the kidney interstitium. Drug induced AIN accounts for 75% of interstitial AKI. Other cases include systemic auto-immune conditions such as SLE or infections by organisms such as *legionella* or Streptococcus species.

Any drug can cause interstitial nephritis. Common drugs associated with AIN include NSAIDs, penicillins, proton pump inhibitors (see Table 3.2). Mechanisms can vary as follows:

- The drug or its metabolites can mimic an antigen that is normally present at the tubular basement membrane or interstitium and induce an immune and inflammatory response
- The drug or metabolite can cause production of antibodies that are deposited in the interstitium as circulating immune complexes leading to a change in intravascular volume and reduced GFR.

Sometimes, humoral and cell-mediated hypersensitivity reactions are mounted against the drug/ metabolite complex affecting both the interstitium and tubules (tubulointerstitial nephritis - TIN). It presents as an allergic reaction (fever, arthralgia, rashes, and eosinophilia) and the immune response within the kidney is not usually dose related. Re-challenge with the drug itself or a similar class of drugs would mount a similar response.

Bacterial and viral induced AIN is similarly caused by an increased immune response to the bacterial/ viral antigens or DNA. This in turn forms immune complexes that can cause a reduction in perfusion, volume and therefore GFR.

The diagnosis of AIN is proven via a biopsy alongside careful history taking to confirm the offending drug. Drug-induced AIN is managed by discontinuation of the offending drug alongside initiation of oral or intravenous corticosteroids. Dialysis may only be necessary in a small percentage of patients – normally those who may also have other underlying conditions that increase the risk of AKI.

3.3 Post-Renal AKI

Post renal acute kidney injury, or obstructive nephropathy, is most commonly caused by a blockage or interruption to the urinary flow, resulting in back pressure on the kidneys and hydronephrosis. It can develop rapidly and requires urgent medical treatment. This section will discuss:

- The structure of the urinary tract
- Common causes of obstruction
- Clinical presentation
- Management of obstruction

3.3.1 Anatomy of the Urinary Tract

Understanding the structure and anatomy of the urinary system is the first step in appreciating where problems arise (Fig. 3.5).

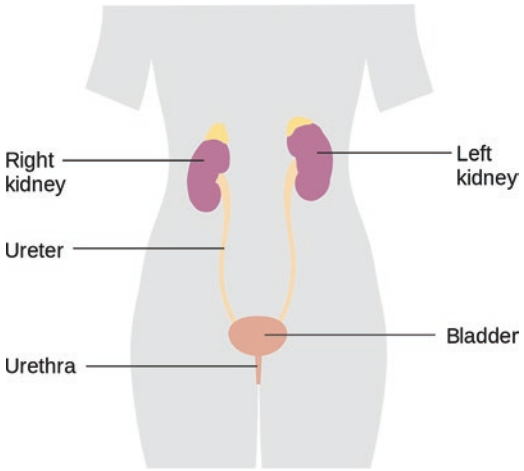

Fig. 3.5 Anatomy of urinary system. (Reused with permission, Cancer Research UK)

The waste produced continuously by the kidneys is dispatched into two ureters. These tubes are 20-25 cm long and lined with smooth muscle cells which contract and relax to aid the transport of urine to the bladder. The bladder itself is a hollow muscular organ, approximately the size of an apple, with flexible walls which expand to accommodate the urine to a capacity of 400-500 ml. The sympathetic nervous system signals the relaxation of the detrusor muscle in the bladder wall while contraction to empty the bladder is in response to parasympathetic nerve stimulation. Internal and external sphincter muscles control the release of urine via the bladder neck into the urethra.

The prostate gland surrounds the male urethra, close to the bladder neck and is covered by a protective capsule. The peripheral zone is located at the back of the prostate and where most of the glandular tissue is found. It is the largest portion of the prostate. The central zone surrounds the ejaculatory ducts and the transition zone sits at the top of the prostate near the neck of the bladder (Fig. 3.6).

3.3.2 Causes of Obstruction

There are a number of clinical conditions which result in obstructive nephropathy. In addition to the common causes discussed below malignancies in the bladder, pelvis, bowel or reproductive system can on occasion present as obstruction.

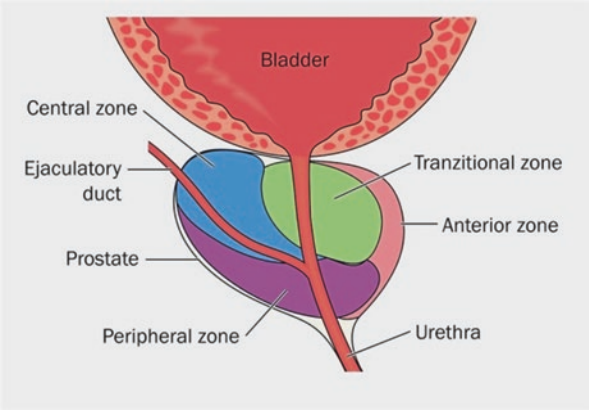

Fig. 3.6 Prostatic zones. (Republished with permission of MA Healthcare Limited, from Management of Prostate Cancer, Eylert et. al., British Journal of Hospital Medicine 73:2, 2012. Permission conveyed through Copyrights Clearance Centre Inc.)

(i) *Benign Prostatic Hyperplasia*

Benign prostatic hyperplasia (BPH) is responsible for approximately 20% of chronic or acute obstructive nephropathy. It is defined as the symptomatic enlargement of the prostate gland and is caused by non-cancerous overgrowth of the epithelial tissue within the transition zone. The incidence of BPH increases with age and 80% of men over 70 years have some degree of hyperplasia on imaging.

Severity of BPH can be assessed using the International Prostate Symptom Score (IPSS); patients are asked to score seven symptoms from 0 to 5 and score their overall quality of life. The symptoms are incomplete emptying, frequency, intermittency while urinating, urgency, weak stream and straining to start urinating. A score of 1–7 is deemed mild, 8–19 moderate and 20–35 severe.

Symptoms arise from several mechanisms. The enlarged prostatic lobes can constrict the urethra, requiring a greater pressure to be created within the bladder to initiate urinary flow, the increased smooth muscle at the bladder neck can prevent the sphincter relaxing enough to facilitate bladder emptying and the detrusor muscles can weaken and malfunction, resulting in acute retention or incontinence. Early medical management with alpha-adrenoceptor blockers can prevent obstruction occurring.

(ii) *Prostate Cancer*

Cancer of the prostate is the most common male cancer in the UK, accounting for 26% of new cancer diagnoses. Tumours develop in the peripheral zone most frequently (70%), with approximately 20% arising in the central zone and 10% in the transitional zone. The incidence of obstructive nephropathy secondary to prostate cancer has been reported as between 3% and 16%, with bladder outlet obstruction being the most common occurrence as the tumour invades the muscular tissue in the bladder neck. Urinary obstruction is a feature of advanced disease and a poor prognostic marker.

(iii) *Kidney Stones*

Urolithiasis or kidney stones are the most common cause of obstructive uropathy. A single stone is unlikely to cause AKI unless the patient has only one functioning kidney but multiple stones are capable of obstructing both ureters.

The prevalence of renal calculi is approximately 10% in men and 7% in women although this gap is closing and the overall incidence is rising. The higher incidence of stone disease in the United States and United Kingdom suggest dietary factors such as obesity, high salt and protein intake are significant. Other risk factors include low urine output, residence in a hot climate, white ancestry and dehydration.

Medicines are responsible for 1–2% of kidney stones but may be regarded as a contributory to many more. The most common causative medicines have been protease inhibitors such as indinavir and atazanavir; sulphonamides, particularly sulfadiazine and sulphamethoxazole; and quinolones such as ciprofloxacin and norfloxacin. Factors that predispose a drug to calculi formation include low water solubility and a high concentration being excreted in the urine. The risk of developing renal calculi increases with the duration of treatment and being prescribed a high daily dose. Patients are at higher risk of developing drug induced calculi if they have a personal history of kidney stones, if they are prone to recurrent urinary tract infections or have defects in their urinary tract system which would promote stagnation of urine.

Stones can develop from a number of substances.

I. Calcium

Stone analysis has found that 80% of renal calculi are composed of either calcium oxalate or calcium phosphate. Hyperoxaluria can occur due to a genetic liver enzyme deficiency or malabsorption of biliary acids, both of which result in excess oxalate in the urine. This can form complexes with calcium which slowly develop into a stone. Elevated levels of calcium in the urine can be a manifestation of hyperparathyroidism, high dietary calcium and salt intake or reduced renal tubular reabsorption. Calcium or vitamin D based medicines such as antacids, phosphate binders or supplements also predispose the patient to stone formation.

II. Cystine

Stones caused by supersaturation of cystine most commonly occur in the congenital condition cystinuria, where the transporter responsible for reabsorption of

cystine, arginine, ornithine and lysine in the proximal tubule is ineffective. Adequate hydration can reduce the incidence of supersaturation and alkalisation of the urine while potassium citrate can aid dissolution and excretion of cystine.

III. Uric acid

Uric acid will precipitate into stones in the presence of low urinary pH. It is responsible for approximately 10% of kidney stones although this can vary with ethnicity. High concentration of uric acid in the urine is also a contributing factor but persistently acidic urine is the key component. This most commonly occurs in patients with metabolic syndromes, type 2 diabetes, obesity and bowel disorders. Drugs that alter the handling of uric acid such as indomethacin, losartan and probenecid can further promote crystallisation. Uric acid nephropathy describes the crystallisation of uric acid in the renal tubules. Increasing the urinary pH with sodium bicarbonate and encouraging oral fluid intake can prevent stone formation in high risk patients.

3.3.3 Clinical Presentation

Presenting symptoms of obstructive nephropathy depend on how acute the onset is. Obstruction that has developed over a period of weeks to months, for example from a prostatic origin, will present with chronic abdominal pain and lower urinary tract symptoms (LUTS) such as urgency, nocturia, hesitation and difficulty initiating micturition. Acute onset obstruction develops rapidly and presents with severe radiating flank pain, haematuria and reduced urine output. Patients may also have more generalised symptoms of nausea, vomiting and fever. If the patient is in acute urinary retention the bladder will also be distended and the patient may be agitated and uncomfortable.

Imaging is required to determine the cause of obstruction or hydronephrosis, either with a renal ultrasound scan or CT of the pelvis. Laboratory tests which should be carried out include urea and creatinine, full blood count, C-reactive protein function. A prostate specific antibody (PSA) and other tumour markers eg CA125, CAE should be checked if there is a suspicion of malignancy.

3.3.4 Management of Obstruction

Initial management of obstruction centres on alleviation of symptoms. Catheterisation is normally required to relieve the pressure on the kidneys and analgesia, antiemetics and intravenous fluids commenced for symptom control. Antibiotics active against gram negative bacteria are required if there is concomitant infection. Urgent surgical intervention with a ureteric stent (a tube inserted into the ureter to hold it open) or nephrostomy (a tube inserted from the skin directly into the kidney to allow

urine to be drained into an external bag) may be necessary if the AKI is severe. This is also indicated if a stone is causing obstruction as the patient is at risk of developing urosepsis or septicaemia; antibiotics are essential in this situation. Longer term management is directed by the underlying disease.

BPH is normally managed medically with alpha-1a adrenoceptor blockers in the first instance, such as tamsulosin, which reduces the tone of the smooth muscle to relax the bladder neck. A 5-alpha reductase inhibitor, for example finasteride, may also be prescribed either alone or in combination with the alpha-adrenoceptor blocker. Finasteride prevents the formation of the androgen dihydrotestosterone which drives prostatic enlargement. Trans-urethral resection of the prostate (TURP) has been the preferred surgical procedure for a number of years but there are now a range of newer alternative surgical options.

Treatment for prostate cancer depends on the PSA at presentation and Gleason (severity) Score and ranges from hormone therapy to radical prostatectomy.

Renal calculi smaller than 5 mm will usually pass naturally with good fluid intake but larger stones may require medical expulsive therapy (MET) with alpha-adrenoceptor blockers to encourage stone passage or extra corporeal shock wave lithotripsy (ECSL) to break down the calculi or ureteroscopy to remove it.

Due to the high risk of recurrence patients should be educated on dietary modifications, for example reducing salt, fat, animal protein and urate and maintaining a daily fluid intake of 2-3 L. Foods with a high content of oxalate should also be limited, which includes nuts, rhubarb and spinach. The American College of Physicians recommends monotherapy with either allopurinol, citrate or a thiazide diuretic to prevent recurrence of calcium-based stones.

Case Study 1

Elsie is an 83 year old woman who has been admitted to hospital with a 2-week history of increasing confusion and lethargy. She has been struggling with oral intake, managing to drink about 500 mL of fluid per day. She has continued to take her regular medications during this time.

She has a past medical history of type 2 diabetes, hypertension and chronic kidney disease stage 3.

Her regular medications are:

- Ramipril 10 mg po od
- Metformin 500 mg po bd

She has no known allergies and does not take over-the-counter or herbal remedies.

On examination she is tachycardic with a heart rate of 105 bpm, and hypotensive with a blood pressure of 80/59 mmHg.

Her respiratory rate is 24 breaths/min, and she is hypothermic at 35.5 °C.

She has reduced air entry bi-basally, and is requiring 2 L/min of oxygen to maintain saturations of 99%.

Her mucous membranes are dry, and her urine output is recorded as 15 mL/hour (oliguria).

An ECG shows sinus rhythm with tented T waves

Her laboratory parameters are as follows:

- Sodium 151 mmol/L (↑)
- Potassium 8.0 mmol/L (↑)
- Urea 50.8micromol/L (↑)
- Creatinine 425micromol/L (↑) – previously 160micromol/L measured 1 month ago
- eGFR 8 mL/min/1.73m^2
- White cell count 25.8×10^9/L (↑)
- Neutrophils 24.6×10^9/L (↑)
- CRP 273 (↑)
- Lactate 5.2 mmol/L (↑)

An initial diagnosis of sepsis is made, presumed secondary to severe community acquired pneumonia, and acute on chronic renal impairment.

Q1 List the possible pre-renal causes of Elsie's acute kidney injury, the mechanisms by which they cause this, and any additional contributory factors.

- Elsie has reduced renal perfusion likely due to sepsis, dehydration (recent poor oral intake) and hypotension.
- Cytokines released as part of the inflammatory response to sepsis cause systemic vasodilatation, increased capillary permeability, decreased systemic vascular resistance, and hypotension. This leads to increased sympathetic nervous system activity, release of renin and vasopressin, and production of angiotensin II. These autoregulatory mechanisms aim to increase cardiac output, produce arteriolar and venous vasoconstriction, and increase salt and water retention with the ultimate goal of increasing tissue perfusion. Arteriolar vasoconstriction occurs predominantly in the renal, splanchnic and musculoskeletal vasculature in an attempt to maintain blood flow to the heart and brain.
- Angiotensin II also produces glomerular arteriolar vasoconstriction, with a greater effect on efferent arterioles than afferent. However, ongoing sepsis and reduced renal perfusion drives further increases in angiotensin II levels, resulting in a more pronounced effect on afferent arteriolar vasoconstriction, leading to a decline in glomerular filtration pressure and development of AKI.
- Elsie's AKI will be exacerbated by ramipril. In addition to worsening hypotension, ramipril will block angiotensin II mediated vasoconstriction of efferent glomerular arterioles, thereby further decreasing the pressure gradient across the glomeruli leading to a drop in GFR.
- Elsie also has a history of chronic kidney disease. This may impair her ability to compensate for a fall in renal perfusion and increases her risk of developing an AKI.

Q2 What should the initial management of Elsie include?

- **Fluid resuscitation**. Elsie's confusion and lethargy has developed over a 2-week period. This suggests her mild hypernatraemia has developed slowly and therefore should be corrected slowly. Her reduced oral intake of both

food and fluid means she will be both salt and water deplete and therefore will require replacement of both. Administration of a crystalloid solution would be the preferred initial choice of fluid replacement. Elsie should be closely monitored for signs of fluid overload (e.g. pulmonary or systemic oedema) during fluid resuscitation.

- **IV calcium gluconate** to stabilise myocardium against hyperkalaemia. Elsie's ECG shows tented T waves which are an early ECG change seen with hyperkalaemia.
- **Insulin and dextrose infusion** to lower serum potassium by driving uptake of potassium into cells.
- **Sepsis 6 bundle**:
  - Oxygen
  - Blood and sputum cultures
  - IV antibiotics
  - IV fluids as above
  - Check serum lactate
  - Monitor fluid balance (input/output)
- **Hold ramipril** – she is hypotensive, hyperkalaemic and has an AKI
- **Hold metformin** – this increases the risk of lactic acidosis in AKI. Monitor blood sugars.

Elsie may also require acute haemodialysis/haemofiltration if she remains oliguric and hyperkalaemic. If she remains hypotensive she may require administration of vasopressors such as noradrenaline.

Case Study 2
James, a frail 76 year old gentleman, is admitted with lower abdominal pain and has not passed any urine for 12 h. On further questioning he describes difficulty initiating urination, hesitancy in flow and having to get up frequently overnight to go to the toilet.

Past medical history:
- Hypertension,
- NSTEMI
- Bowel cancer.

Weight:
- 62 kg

Medication history:
- Aspirin 75 mg in the morning
- Atorvastatin 40 mg at night
- Ramipril 5 mg at night
- Bisoprolol 10 mg in the morning
- GTN spray when required
- Paracetamol 1 g when required
- No known drug allergies

Q1. What are your initial thoughts on the possible causes of James' symptoms?
A1. Given his age he is high risk of BPH and prostate cancer and has developed obstructive uropathy. There is also a possibility that his bowel cancer has returned.
Q2. What tests or investigations do you think should be carried out?
A2. Urea and creatinine, full blood count, liver function tests, C-reactive protein, PSA, CT of abdomen and pelvis, observations (temperature, respiratory rate, blood pressure)

Relevant results:
- BP 115/58
- HR 55 bpm
- Temp 36.5C
- RR 20
- Sodium 136 mmol/l
- Potassium 5.3 mmol/l
- Urea 14 mmol/l
- Creat 180 mmol/l (baseline 85 mmol/l 3 months earlier)
- eGFR 27
- PSA 6.2 ng/ml

CT has diagnosed BPH. James has been catheterised and is now passing urine. He has been prescribed intravenous fluids and has been referred to urology for review.

Q3. What long term treatment do you advise for management of BPH?
A3. Given a slightly low baseline blood pressure finasteride 5 mg daily would be more appropriate than tamsulosin for initial treatment.

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Chapter 4
Chronic Kidney Disease and End Stage Renal Disease

Dan Martinusen

Abstract This chapter will describe the practice essentials that are considered standard of care, common conditions and their treatments. While many might consider nephrology pharmacy is all about the "dose", it is far more encompassing than that. The practicalities of obtaining a best possible medication history, reconciling discrepancies and removing barriers to adherence will be discussed as part of good pharmacy practice. Further, opportunities for pharmacists to develop or coordinate population-based interventions will be discussed. Pharmacists develop evidence-based prescribing algorithms that both support best practice and the deprescribing of less effective therapies. The benefits of deprescribing include less cost, tablet burden and likely a reduced falls risk. This "medication management" is patient-centred care that optimizes safe, effective, appropriate drug therapy.

The typical goals of care for a patient with advanced kidney disease (under 30 mL/min estimated glomerular filtration rate (eGFR)) include achieving target blood pressure, target weight, normalizing most bloodwork and reducing symptom burden. In so doing, we hope to improve quality of life, slow the progression of kidney disease and reduce the risk of falls. An important goal is to smooth transitions in care, should a patient go on to transplant or dialysis. Finally, if a patient chooses not to transition and their journey ends, we want to improve their quality of death.

The patient journey through kidney disease may take place over many years. Initially the health care system screens the patient for chronic kidney disease risk factors such as diabetes, hypertension, age over 60 and family history. If the patient

D. Martinusen (✉)
Faculty of Pharmaceutical Sciences, Royal Jubiliee Hospital, Vancouver Island Health Authority, University of British Columbia, Victoria, BC, Canada

Pharmacy, British Columbia Renal, Vancouver, BC, Canada
e-mail: Dan.Martinusen@viha.ca

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is at risk, we try to reduce the risk through modifiable factors. Initial kidney disease is diagnosed and treated as are comorbid conditions. As kidney disease progresses, as identified by serial eGFR measurements and albumin creatinine ratios, the team will treat complications and prepare the patient for renal replacement therapy. This may include a transplant workup, informed decision around dialysis modality, creating a vascular access or choosing conservative care. For the individual patient, any one of these may be a valid informed choice. Our job is to advocate for our patient, optimize and align drug therapy to that choice. It is quite possible for a patient to have a 30 year life expectancy once in renal failure whereas for others it could be considerably shorter.

Keywords Kidney · Renal insufficiency – chronic · Pharmacotherapy · Nephrology · End stage renal disease · Polycystic kidney disease · Anaemia · Dyslipidaemia

A new pharmacist can be overwhelmed when introduced to the care of a patient with advanced kidney disease. These patients often have multiple comorbidities, are on many medications and frequently require hospitalization. These patients are not just kidney disease patients. They often have endocrine, cardiac, geriatric conditions and are frail. They commonly present with limited finances, adherence issues and high social needs. In short, this patient population presents a complex challenge for the pharmacist. The individual who chooses this field is drawn to working to the full scope of their practice and abilities and enjoys complex problems. The pharmacist must be a strong patient advocate and serve as an information resource. However, the professional satisfaction gained from working with a truly interdisciplinary team and achieving positive patient outcomes at the individual and population level cannot be overstated.

The pharmacist will also learn of the therapeutic controversies in nephrology where there is equipoise in the evidence base. Knowledge of these controversies is an important competency of the renal pharmacist as is discerning the difference between evidence and opinion. The pharmacist can engage with other clinicians on the relative merits of continuing or discontinuing a therapy, but should remain respectful of opposing opinions.

Up to 11% of the general population has kidney disease (Webster et al. 2016). Roughly 3% will have a normal eGFR but abnormal urine, 3% will have an eGFR between 60 and 90 mL/min. 4.3% of patients fall into a range where decisions of dose reductions are made; 30–60 ml/min. Only 0.2% of the population has kidney function less than eGFR 30 mL/min but this last group is the nephrology pharmacist's focus. Most pre-dialysis or "kidney care" clinics will generally define their service as 30 mL/min or below. Exceptions may include some hereditary or autoimmune disorders. It should be noted that many patients are managed by family physicians or residential care physicians, particularly if conservative care is the chosen path. Nephrology may become involved if care needs change.

The leading causes of kidney disease are diabetes, responsible for 45% and hypertension with 27% (Webster et al. 2016). The natural history of diabetes leads half of patients to develop proteinuria in 15–20 years and half of those patients going on to develop renal failure 5 years later (Hasslacher et al. 1989). Hypertensive nephrosclerosis can be mitigated through good blood pressure management. Likewise, long term control of diabetes to guideline can mitigate the risk of end stage complications such as nephropathy, neuropathy and retinopathy. However, patient non-adherence continues in these populations and we will typically see the result in our clinics. Furthermore, may continue to smoke, have poorly controlled lipids, poor dietary habits and have an unhealthy weight. Working with these patients to discover the motivation and execute a plan to achieve goals is ongoing work. Motivational interviewing with cultural sensitivity can be a powerful tool.

Hereditary kidney disease may affect young children or develop later in life. Pediatric discussion is beyond the scope of this chapter. In the adult population, the predominant inherited condition is autosomal dominant polycystic kidney disease (ADPKD). Recently, medications have become available which may slow the progression of this disease and delay the time to dialysis. The pharmacist should become familiar with emerging therapies such as these and be part of the discussion.

A group of autoimmune diseases come under the heading of glomerulonephritis and therapy typically comprises of various immune-modulating drugs. 8% of kidney disease is the result of glomerulonephritis and these patients are being seen increasingly in the multidisciplinary kidney care clinic. Pharmacists can and should play a role in creating best-practice algorithms to standardize care to the evidence base. Not only does such involvement improve outcomes but stewards the most appropriate and cost effective use of these agents.

Finally, drug induced kidney injury interstitial nephritis or acute tubular necrosis comprises at least 4% of kidney disease. Proper counselling to avoid certain drugs until the patient recovers from volume depletion is essential. Counselling to minimize use of or avoiding other medications including non-prescription medication is very important. In most countries, patients may purchase non-steroidal anti-inflammatories, oral decongestants and sugar laden liquids without a prescription and may suffer renal consequences.

4.1 Major Causes for Chronic Kidney Disease and Management

4.1.1 Diabetes

4.1.1.1 Epidemiology

Diabetes mellitus is the leading cause of chronic kidney disease (Cheung et al. 2017). Diabetic nephropathy develops in 35–45% of patients with type 1 DM and 20% of type 2 DM (Canadian Journal of Diabetes 2011).

4.1.1.2 Pathophysiology

Diabetic nephropathy is caused by multiple mechanisms of insults. First, hyperglycemia causes an increase in the osmotic pressure, which increases afferent arteriolar blood flow and glomerular capillary pressure (Canadian Journal of Diabetes 2011). As well, diabetics have an increased responsiveness to Angiotensin 2, which causes vasoconstriction and increases glomerular capillaries pressure (Canadian Journal of Diabetes 2011). Increase in the glomerular pressure and an increase proteinuria result in mesangial hypertrophy and cellular injury, contributing to glomerulosclerosis. As the number of functional nephrons is decreasing, the remaining nephrons try to compensate by increasing their filtration capacity, which is called hyperfiltration. Hyperfiltration contributes to the progressive sclerosis of the glomeruli and renal failure (Canadian Journal of Diabetes 2011).

Other risk factors for diabetic nephropathy progression are hypertension, elevated cholesterol, albuminuria, increased BMI, advanced age and smoking (James et al. 2014).

4.1.1.3 Management

First of all, even if the evidence for benefits is minimal, lifestyle interventions are very important in this population. It is recommended that diabetic patients have a healthy weight, do regular exercise and have a balanced diet low in sodium and carbohydrate (James et al. 2014; Soroka et al. 2017).

Numerous studies show that hyperglycemia is linked to CKD development and its progression. In the ARIC study, each 1% increases in HbA1c was associates with a 31% higher risk of CKD (Han et al. 2015). In general, HbA1c < 7% is recommended for diabetic patients with nephropathy according to guidelines (Cheung et al. 2017; KDIGO 2012). However, it is worthwhile to note that HbA1c has its limitation in CKD patients since this result can be influenced by factors, such as: the patient's reduced red cell survival, the use of erythropoietin stimulating agents and the mechanical destruction of red blood cell during dialysis. For all these reasons, clinicians need to rely more on home blood sugar monitoring to assess their intervention (Cheung et al. 2017).

There are currently a growing number of diabetic therapeutic options to meet target HbA1c. Metformin is an efficacious and cost-effective therapy which is often under-utilized in CKD patients because of the risk of lactic acidosis. More recently, guidelines suggest its use down to an eGFR of 30 mL/min, especially if patient is aware to hold the medicine in period of dehydration (Cheung et al. 2017). SGLT-2 inhibitors and GLP-1 agonists have now trials showing that they have kidney protective effect as well as cardiovascular benefits. However, SGLT-2 inhibitors are not indicated in CKD stage 4 and 5. Additional trials are currently ongoing to with renal primary endpoints in this population (Cheung et al. 2017; James et al. 2014; Judd and David 2015). Sulfonylurea agents have been used in CKD patients for decades. They are associated with an increased risk of hypoglycemic episode, especially

since parent drug and metabolite can accumulate. Thiazolidinediones use has been decreasing due to risk of fluid retention and heart failure exacerbation. DPP-4 inhibitors may require drug dosage adjustment dependent on kidney function and clinicians need to be vigilant with the possible increase risk of heart failure. Finally, insulin often becomes the only therapeutic options possible for diabetic patients with low kidney function. The risk of hypoglycemic episode in this population is quite high, considering that a decreased kidney function will prolong the half-life of insulin (Cheung et al. 2017; Soroka et al. 2017; Judd and David 2015).

Blood pressure control helps to manage proteinuria as well as decreasing cardiovascular disease (Cheung et al. 2017; KDIGO 2012). Guidelines for blood pressure management in diabetic CKD disease is based on expert opinion, but generally recommend 130/80 (for more information on blood pressure management, please refer Sect. 1.2) (Cheung et al. 2017; James et al. 2014; Judd and David 2015; Perkovic et al. 2016). Angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) are usually considered first line agents, as they will help with the management of blood pressure as well as decreasing proteinuria (Cheung et al. 2017; KDIGO 2012; Davies et al. 2018).

4.1.2 Hypertension

4.1.2.1 Epidemiology

Hypertension is the second leading cause of CKD in the United States (Schrier et al. 2014). However, hypertension is found in 80–85% of all CKD patients, with its prevalence increasing with the worsening of the kidney function (Garber et al. 2018). Uncontrolled hypertension is associated with higher risk of CKD progression and rate of end-stage renal disease, as well as a higher risk of cardiovascular complications, including stroke and heart disease (Perkovic et al. 2016; Garber et al. 2018). Resistant hypertension, as well as nocturnal hypertension has been seen more frequently in CKD patients and is associated with an increased risk of CKD progression. While the average blood pressure (BP) drops about 15% overnight, a subset of patients, called “non-dippers”, have their BP measurement failing to drop >10% of their average daytime BP. The rate of “non-dippers” is higher among the CKD population and it has been associated with increased risk of cardiovascular events and progression to end-stage renal disease (Disease-a-Month 2003).

4.1.2.2 Pathophysiology

Hypertension has a unique relation with CKD since they are both a cause consequence of each other (Orr et al. 2018). Hypertension in CKD is multifactorial. Physiologic changes in CKD result in fewer functional nephrons and abnormal tubular function leading to decrease sodium excretion. This results in water retention

and an increase in BP. There is also hypothesis that sodium causes hypertension by increasing inflammation, oxidative stress and arterial stiffness (Orr et al. 2018).

In CKD patients, the renin-angiotensin-aldosterone system (RAAS) is excessively active, likely due to renal ischemia. The renin, which is usually released during a period of decrease renal perfusion, leads to release of angiotensin II which causes vasoconstriction, secretion of aldosterone triggering sodium and water retention as well as an increase in the sympathetic system activity (Orr et al. 2018).

Patients with CKD also have inappropriate increased sympathetic activity for their effective volume status. The exact mechanism for this imbalance is not well understood (Garber et al. 2018).

4.1.2.3 Management

Target BP for CKD patients is quite a controversial topic. Guidelines by different medical societies suggest different goals of therapy depending on the literature use to establish their recommendations, as discussed in Table 4.1 (KDIGO 2012; Judd and David, 2015; Perkovic et al. 2016; Schrier et al. 2014; Orr et al. 2018). A subgroup of the SPRINT trial looked at BP target in CKD non-diabetic patients. CKD patients enrolled in the intensive blood pressure group (systolic BP < 120 mmHg) had 19% less major cardiac events and a decrease of all-cause mortality of 28% compared to the standard of care (systolic BP < 140 mmHg) group after a median follow-up of 3.3 years (Sommerer and Zeier 2016). Lower BP target may improve CKD patients' outcomes if the intensive target and antihypertensives are tolerated well.

Lifestyle changes may make an important impact on CKD patients BP, especially dietary salt restriction. High salt intake (> 4.6 g/day) has been associated with an increase in proteinuria as well as a decrease in renal function. Furthermore, a low sodium diet (< 2 g/day) will maximize the antiproteinuric and antihypertensive effects of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor

Table 4.1 Summary of blood pressure targets for CKD patients according to guidelines

Guidelines	CKD population specification	Blood pressure target recommended (mm Hg)
KDIGO 2012 (KDIGO 2012)	Urine albumin <30 mg/day	**< 140/90**
	Urine albumin >30 mg/day	**< 130/80**
JNC 8 (Schrier et al. 2014)	All CKD pts	**< 140/90** (if older than 60 y/o, < 150/90 is appropriate)
ADA 2018 (Han et al. 2015)	DM patients	**< 140/90**
	DM patients with high cardiovascular risk (including albuminuria)	**< 130/80 if tolerated**
ACC/AHA 2017 (Garber et al. 2018)	All CKD patients	**< 130/80**
CDA 2018 (Soroka et al. 2017)	DM patients	**< 130/80**

blockers (ARBs) (Perkovic et al. 2016; Garber et al. 2018). Even if the data is lacking, increasing cardiovascular exercise, maintaining a healthy weight (BMI 20–25) and limiting alcohol intake to 2 drinks/day for men and 1 drinks /day for women is also believed to help with BP management (Perkovic et al. 2016; Garber et al. 2018).

ACEis and ARBs are the cornerstone for BP management in CKD patients. ACEi and ARB have been shown to decrease effectively BP, decrease CKD progression as well as decrease in proteinuria (Perkovic et al. 2016; Schrier et al. 2014; Garber et al. 2018). Generally, ACEi and ARB are thought to have similar efficacy (Perkovic et al. 2016; Garber et al. 2018). However, it is not recommended to combine ACEi and ARB for BP management since the ONTARGET study has shown that this dual therapy is associated with adverse reactions like hyperkalemia, hypotension and worsening kidney function (Yusuf et al. 2008).

Other therapeutics options for blood pressure management include diuretics, which are also often used for managing edema. Thiazide diuretics are generally less efficacious if eGFR <30 mL/min. If the kidney function is below this threshold, loop diuretics become the preferred agents to manage edema. However, diuretics are to be used cautiously in patients at high risk of acute kidney injury (AKI). Calcium channel blockers are usually considered second line therapy in CKD patients. For patients with proteinuria, non-dihydropyridine calcium channel blockers (diltiazem and verapamil) can help to decrease proteinuria. Aldosterone-antagonists have antiproteinuric effect as well. However, they are to be used with caution in patient with decrease kidney function due to the risk of hyperkalemia and acute kidney injury (Perkovic et al. 2016; Garber et al. 2018).

4.1.3 Polycystic Kidney Disease

4.1.3.1 Epidemiology

Polycystic kidney disease (PCKD) is the most common inherited kidney genetic disease (Peh 2013; Tseng and Preminger 2013). PCKD is defined by enlarged kidneys covered by multiple renal cysts, liver cysts and increased risk of intracranial aneurysm (Peh 2013; Tseng and Preminger 2013). This genetic disorder has been identified in all races. Between 45% and 70% of patients with PCKD will reach end-stage renal disease (ESRD) by the time they are 65 years old (Tseng and Preminger 2013).

4.1.3.2 Pathophysiology

PCKD is characterized by fluid filled cysts developing on the kidneys (Peh 2013; Tseng and Preminger 2013; Torres et al. 2017). As the cysts grow, an inflammatory response is developed around the cysts (Torres et al. 2017). The fluid filled cyst can cause urine stasis, which contribute to the increase risk of pyelonephritis, kidney

abscess, as well as kidney stones. Cyst hemorrhage can also occur. Reduction in urinary concentrating ability and excretion of ammonia occurs early in this population, which likely also contributes to the development of uric acid and calcium oxalate stones (Torres et al. 2017). Urinary concentration defect also increases concentration of vasopressin, which contributes to cysts growth (Torres et al. 2017).

Typically, renal function starts to decline about 12 years after cysts appear. However, once kidney function starts to decline, the decrease in eGFR is quite rapid with an average loss of kidney function between 4 and 6 ml/min/year (Peh 2013).

Abdominal pain is a common symptom in this population. Acute pain can be due to the cyst's ruptures, stones or infections (Torres et al. 2017). Chronic pain is mostly due to the enlarged kidneys (Torres et al. 2017).

4.1.3.3 Management

AMPc modulation by targeting the vasopressin V2 receptor can impact PCKD progression by decreasing cysts growth. Tolvaptan, which is a Vasopressin V2-receptor antagonist, has been studied with two randomized trials in the PCKD population. TEMPO 3:4 study looked at tolvaptan use in PCKD patients with preserved kidney function with a follow-up over 3 years. In this study, tolvaptan slowed down the increase in kidney volume from 2.8%/year to 5.5%/year for patient untreated (Urinary Obstruction 2016). The second trial, REPRISE trial, studies tolvaptan use for 1 year in PCKD patients with reduced kidney function. In this population, tolvaptan slowed down the rate of kidney function decline from 3.61 to 2.34 mL/min/year (Bash et al. 2008). The clinical data currently available for tolvaptan are still limited in terms of which population will benefit the most from this intervention, tips on improving its tolerability, when should this intervention be stopped, and the impact of long term use (the longest RCT followed patients for 3 years). The tolerability profile of the drug is also challenging; a significant percentage of patients are unable to tolerate it due to excessive thirst, polyuria and fatigue (Peh 2013; Urinary Obstruction 2016; Bash et al. 2008). Furthermore, increased liver enzymes and possible liver toxicity has been reported with tolvaptan, recommending a very close follow-up of patients' liver enzymes for at least 18 months after starting the treatment (Peh 2013; Urinary Obstruction 2016; Bash et al. 2008).

A high water intake targeting a urine osmolality $\leq$250 mOsm/kg, low salt diet and avoiding caffeine may also help to decrease cyst progression by suppressing vasopressin secretion, but this intervention has not been proven in clinical trials (Sakhaee et al. 2012).

Hypertension develops usually before eGFR decline in this population. Early detection and treatment of hypertension is very important in this population, since cardiovascular disease is the main cause of death (Peh 2013; Torres et al. 2017). Hypertension in this population accelerate increase in proteinuria and the loss of kidney function, increases the risk from cardiovascular disease, valvular disease and aneurysm (Torres et al. 2017). In general, a lower blood pressure is considered better for this population. The HALT-PKD study found that, in a group of patients with

preserved kidney function, a BP target between 95–110 and 60–75 decreased kidney volume growth in comparison to patient with target BP between 120–130 and 70–80. However, no change in kidney function was observed in this study (Pyram et al. 2012). ACEis have been shown to reduce proteinuria in this population, which explains why ACEis/ARBs are usually considered first line of therapy in this population (Peh 2013).

Renal pain is common and due to cyst hemorrhage, nephrolithiasis, cyst infection and rarely tumor. Pain can be acute/severe pain, but also some chronic discomfort and sensation of fullness. Pain is usually managed conservatively with non-opioid pain killer. In case of severe pain, opioid agents may be appropriate (Torres et al. 2017).

About 20% of PCKD patients will have nephrolithiasis, majority of the stones being calcium oxalate and uric acid (Torres et al. 2017). For prophylaxis and treatment of nephrolithiasis, please refer to Sect. 1.4.

Renal cyst infection accounts for about 9% of hospitalization in PCKD patients. When treating urinary tract infection (UTI) in this population, consider the capacity of the antibiotic for cyst penetration, since this population is at higher risk for complicated UTI. Fluoroquinolone, trimethoprim-sulfamethoxazole, clindamycin, vancomycin and metronidazole are antibiotics with good cyst penetration (Torres et al. 2017).

4.1.4 Obstruction

4.1.4.1 Epidemiology

Obstruction is a common problem causing acute as well as chronic kidney disease. Signs of obstruction are usually mild and occur over a long period of time, but early recognition is helpful to prevent loss of kidney function (Colantonio et al. 2018). One of the main causes of obstruction is nephrolithiasis (kidney stones), but obstruction can also be related to tumor, benign prostate hyperplasia and renal polyps. This section will focus on nephrolithiasis.

4.1.4.2 Nephrolithiasis (Kidney Stones)

Kidney stones can develop anywhere along the urinary tract, and obstruction to the urinary tract system develop depending on the stone size and location (Torres et al. 2009). Typical stones are usually composed of calcium oxalate, calcium phosphate, uric acid or struvite (Torres et al. 2009). Table 4.2 summarizes the cause and management of the most frequent type of kidney stones (Yusuf et al. 2008; American Diabetes Association 2018).

Most patients presenting with nephrolithiasis will have acute flank/back pain, dysuria and hematuria, nausea/vomiting. Acute management of kidney stones

Table 4.2 Summary of stone type, cause and prophylactic management (Yusuf et al. 2008; American Diabetes Association 2018)

Stone type	Causes	Prophylactic treatment
Calcium oxalate	Hypercalciuria, ↑ sodium intake, ↑ protein intake	↑ fluid intake, ↓ oxalate and ↓sodium intake in diet Chlorthalidone
Calcium phosphate	Alkaline urine, hyperparathyroidism	↑ fluid intake
Uric acid	Acidic uric, diet high in purine, gout	↑ fluid intake, ↓ purine intake in diet, Xanthine oxidase inhibitor
Struvite	Urinary tract infections (UTIs), ↑ urine pH, certain microorganisms	Antibiotics

consists on maintaining a good hydration and pain management. Some stones may pass spontaneously, while other will need lithotripsy or urethroscopy to allow stone removal (Torres et al. 2009). It is important to note that some medications (ethylene glycol, indinavir, methotrexate, or sulfonamides) can cause crystals depositions in the tubulointerstitium and lead to urinary obstruction (Colantonio et al. 2018).

4.1.5 Glomerulonephritis

Glomerulonepritis (GN) refers to inflammation in the glomerulus of the kidney. GN encompasses many different conditions such as lupus nephritis, ANCA vasculitis, membranous nephropathy, FSGS and minimal change disease. All these conditions can cause scarring in the glomerulus, which can precipitate kidney damage and kidney failure (Canadian Journal of Diabetes 2011). Proteinuria, hematuria, hypoalbuminemia, hypertension and edema are the usual signs of GN. These disorders can be idiopathic (primary) or secondary to another condition like, infections, cancer, medications, diabetes or hypertension (Harris and Torres 2018). A kidney biopsy is needed to establish the diagnosis (Canadian Journal of Diabetes 2011). Treatment of GN is usually divided into 2 main objectives: 1. To control the inflammation with immunosuppressants, 2. To control proteinuria with antiproteinureic agents (ACEi/ARB) (Harris and Torres 2018). Complications specific to GN patients also need to be managed, which include hypertension, dyslipidemia, hypercoagubility, increase risk of infection and edema (Harris and Torres 2018). This section will discuss briefly immunosuppressive treatment four of the most common GN.

4.1.5.1 ANCA Vasculitis

ANCA vasculitis is described by inflammation causing necrosis in small vessels, including the capillary in the kidney, but can affect also other systems (upper/lower respiratory system, nervous system, skin, eyes) (Harris and Torres 2018). This disease is usually very aggressive with a quick decrease in kidney function and high

mortality if treatment is not provided (Harris and Torres 2018). Therefore, treatment with immunosuppressants is needed for these patients. The therapeutic plan usually consists of an induction therapy with steroid and cyclophosphamide or rituximab, followed by a maintenance therapy of at least 18 months with azathioprine, mycophenolate mofetil, or rituximab for patients with renal involvement.

4.1.5.2 IgA

IgA GN is diagnosed by IgA staining in the glomeruli on a kidney biopsy (Cheung et al. 2017). The clinical presentation of this disease varies tremendously, from patients having a low level hematuria and proteinuria, to patients with aggressive disease progressing to end-stage renal disease quickly (Harris and Torres 2018). Antiproteinuric agents are the main treatment in patient with low-grade proteinuria (< 1 g/day). For patient with more aggressive disease, steroid or steroid/cyclophosphamide treatment can be used (Harris and Torres 2018).

4.1.5.3 Lupus Nephritis (LN)

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease which can affect many organs, including the kidneys. In adults, 50–60% with SLE will present some renal involvement. This percentage increases to 80% in the pediatric SLE population (Canadian Journal of Diabetes 2011). Renal biopsy will guide therapeutic choice by informing the clinician on the lupus nephritis class and activity (active vs. chronic disease). Treatment usually consists of an induction (usually cyclophosphamide or high dose mycophenolate mofetil) and a maintenance phase (Yusuf et al. 2008). The following immunosuppressive agents can be used: cyclophosphamide, steroid, mycophenolate, CNIs, azathioprine (Harris and Torres 2018).

4.1.5.4 Membranous Nephropathy

Membranous is generally an adult disease. It is characterized by immune complexes deposit in the subepithelial area, leading to the thickening of the glomerular basement membrane. The small vessels in the kidney become damaged, which induced proteinuria and can lead to nephrotic syndrome (Canadian Journal of Diabetes 2011). Initial treatment of this condition consists of ACEi/ARB, diuretic and a low sodium diet to control edema. No immunosuppressive treatment is usually necessary at presentation since 20% of patients will go into spontaneous remission without any other intervention (Harris and Torres 2018). If there is important change in the patient's kidney function (increase of serum creatinine by more than 30%) or proteinuria persists at level > 4 g/day beyond 6 months of antiproteinuric therapy, immunosuppressive therapy (cyclophosphamide/steroid; calcineurin inhibitors, rituximab) is then considered (Harris and Torres 2018).

4.2 Slowing the Progression and Protecting Existing Kidney Function Beyond Diabetes & Blood Pressure

With increasing incidence and prevalence of chronic kidney disease (CKD) and longer survival of patients with disease states that may contribute to CKD, another focus that needs to be reviewed are modifiable risk factors to help slow the progression and protect existing kidney function beyond diabetic and blood pressure controls.

4.2.1 Smoking Cessation

Smoking remains a major public health problem despite substantial data associating it with death, cancer, cardiovascular diseases, respiratory diseases and chronic kidney disease. Nicotine directly stimulates the postganglionic sympathetic nerve endings to increase plasma levels of norepinephrine and adrenaline thereby increasing peripheral vascular resistance (Grassi et al. 1994). Other vasoconstrictors such as arginine vasopressin and endothelin-1 are also increased during nicotine inhalation (Gambaro et al. 1998; Halimi et al. 1998). Besides nicotine, heavy metals such as cadmium and lead are inhaled during smoking and may promote kidney tubular injury. Cadmium in particular has been shown to accumulate in proximal tubule epithelial cells resulting in polyuria and proteinuria (Prozialeck et al. 2009). The oxygen free radicals and prothrombotic factors associated with smoking may play a role in a downstream change for renal failure as well. Tobacco and cigarette smoke Induces the production of advanced glycation end products (AGEPS) and may be responsible for vascular permeability to accelerate vasculopathy in renal disease (Makita et al. 1991, 1994; Cerami et al. 1997).

Despite numerous studies' hypotheses on the exact mechanism nicotine exerts its harmful effects, there are still several aspects of smoking-induced renal damage that are unclear. Four systematic reviews have evaluated smoking as a risk factor for incidence of CKD with the most recent meta-analysis concluding that the relative risk of incident CKD is 1.27 (95% CI 1.19–1.23) for ever-smokers, 1.34 (95% CI 1.23–1.47) for current smokers and 1.15 (95% CI 1.08–1.23) for former smokers (Xia et al. 2017; Jones-Burton et al. 2007; Noborisaka 2013; Elihimas Júnior et al. 2014).

Functional data have demonstrated that nicotine significantly affected intra-renal changes by reducing renal plasma flow by approximately 100 and 80 mL/min per 1.73 m^2 from chronic and ex-chronic smokers respectively in one study (Gambaro et al. 1998). Another study of 35 healthy normotensive IgA glomerulonephritis patients investigated effects of smoking versus sham smoking. The study measured renal clearance with radioactive indium and found an acute statistically significant decrease in glomerular filtrate rate (GFR) ($P < 0.005$) and increase in renovascular resistance in the nicotine group (Ritz et al. 1998). Active smoking is an independent

factor for albuminuria that is directly related to the number of pack years and was calculated to account for a four-fold higher prevalence compared to non-smokers (Gupta et al. 2014; Wachtell et al. 2002; Gerstein et al. 2000).

Morphopathologic alterations from smokers have also been investigated for evidence of renal dysfunction secondary to nicotine. One study of 567 patients found significant correlation between smoking and myointimal hyperplasia of arterioles in male and patients over 50 years old (Lhotta et al. 2002). Diabetic patients who had more than 20 cigarettes per day were found to have a thickening of the glomerular basement membrane on renal biopsies (Baggio et al. 2002).

The most studied relationship has been amongst the role of tobacco in patients with diabetes. In patients with type 1 diabetes, smoking is found to increase risk of developing nephropathy and is proportionately increased with the number of cigarettes smoked (Christiansen 1978; Telmer et al. 1984). In this population, smoking increases incidences of microalbuminuria and proteinuria, reduces interval between microalbuminuria to persistent proteinuria and increases rate of progression to end stage renal failure (Chase et al. 1991). A systematic review and meta-analysis of 88 prospective studies looked at the risk of different smoking behavior with risk of type 2 diabetes (Pan et al. 2015). The pooled relative risk of type 2 diabetes was 1.37 (95% CI 1.33–1.42) for current smokers and non-smoking; 1.14 (1.10–1.18) for former smoking and never smoking and 1.22 (1.10–1.35) for never smokers with and without exposure to passive smoke. Furthermore, a dose-response relation for current smoking and diabetes risk was found for light, moderate and heavy smokers that was again confirmed by another group in Japan (Akter et al. 2017). Unfortunately neither study commented on end organ damage or microalbuminuria secondary to the diabetes.

The implications regarding smoking and worsening renal function and pathology are numerous and though it would seem conceivable that cessation would have benefits, it is still best to characterize them. Population based retrospective study of 65,589 Norwegian patients with a follow up of 10.3 years saw their kidney failure risk significantly decrease with increased elapsed years since smoking cessation (Hallan and Orth 2011). Patients who quit smoking for ≥20 years had a HR 8.84 (95% CI 1.70–45.6) compared to 10.5 (1.32–82.3) for those who quit for 1–4 years for risk of kidney failure in men below 70 years old (Hallan and Orth 2011). A Singaporean retrospective cohort study of 63,257 followed for 13.3 years demonstrated that the risk of kidney failure remained significant in patients who had quit smoking for 1–9 years (adjusted HR 1.83 [95% CI 1.29–2.6]) but the risk decreases when patients had stopped smoking for greater than 10 years to almost baseline (adjusted HR 1.02 [0.71–1.47]) (Jin et al. 2013). Robust renal registries have allowed for several population based retrospective studies and their results in showing the significance of smoking status to kidney failure have been consistent in direction. Prospective studies though often shorter due to funding have also shown the same relationship as well. Thirty five type two diabetic patients with a baseline median of 41 pack years were followed at a smoking cessation program over 2 years (Hieshima et al. 2018). After 12 months, patients who had microalbuminuria at baseline had none in the smoking cessation group compared to the non-smoking

group (75.5 ± 96.3 mg/gCr [−19.7 mg/gCr] vs 97.7 ± 90.4 mg/gCr [+35.8 mg/gCr]). The eGFR was unchanged after 12 months in the two groups though the authors attributed that to the short follow-up as eGFR improvements is expected at an approximate rate of 0.18 mL/min/1.73m^2/month per 10 mmHg decrease in mean arterial pressure and the study saw a 9 mmHg decrease by the end of the 12 months in the smoking cessation group (Maki et al. 1995). Another larger group of 193 newly diagnosed diabetic patients were encouraged to stop smoking and within 1 year, patients had improvements of glycemic and lipid profiles, reduction in blood pressure, decrease in prevalence of microalbuminuria that were independent of pharmacological or lifestyle changes (Voulgari et al. 2011). The prevalence of microalbuminuria was statistically significant by 50.1 ($p < 0.001$) patients. Again, the eGFR difference between the two groups was not statistically different 117.2 vs 114.9 mL/min 1.73m^2 ($p = 0.08$) at the 1 year.

Smoking cessation is an important and inexpensive intervention in preventing progression of CKD. As pharmacists, we play a pivotal role in helping patients select the best smoking cessation therapy especially since most of these substitutes are available without prescription. Pharmacists are widely accessible and guidance and encouragement are required during this time along with frequent reassessment as existing renal impairment may impact potential under-dosing or overdosing of some of these agents. Studies with pharmacist-led smoking cessation programs have demonstrated quit rates similar or higher than other health professionals and often to be most cost-effective as well (Saba et al. 2014; Shen et al. 2015; Csikar et al. 2016). In Canada, pharmacist-led smoking cessation programs have been implemented in most provinces and in the United States at least 17 states have passed legislation for pharmacists for autonomous prescribing for smoking cessation medications as well. By increasing availability, convenience and options, smoking cessation is an easily targetable modifiable risk factor for preventing or improving kidney disease.

4.2.2 Exercise

Physical activity is defined as any bodily movement produced by skeletal muscles that result in energy expenditure. It can be further classified as either resistance or aerobic exercise (Caspersen et al. 1985). In the general population, it is widely accepted that physical activity has metabolic benefits associated with lower risks of coronary heart disease, stroke and cardiovascular death. Conversely, a sedentary lifestyle promotes adiposity, insulin resistance and hypertension that may directly injure the kidney (Klausen et al. 2007; Chen et al. 2004). Patients with CKD suffer from impaired exercise tolerance and performance with a decline from expected norm of 70% at early stages of CKD to 50% of decline when starting dialysis therapy (Heiwe and Jacobson 2011). Renal anemia, malnutrition, polyneuropathy and

vascular dysfunction are some of the underlying causes of this exercise limitation. In early stages of CKD, aerobic exercise may stimulate vascular and renal baroregulatory systems through vasodilation of the efferent renal arteriole for downstream regulation of the renin-angiotensin system (Bergamaschi et al. 1997). In hemodialysis patients and non-dialysis dependent CKD patients, exercise training can beneficially modify arterial stiffness (Mustata et al. 2004, 2011). The exact mechanisms responsible for the improvement or slowing in kidney disease progression as a result of exercise are still not fully understood. Metabolic disturbances are highly prevalent in CKD patients and diabetes, obesity and hypertension may further contribute to these derangements. Aerobic exercise may slow or reverse some of these metabolic processes with benefits that may confer to benefits to kidney function either directly or indirectly through improvement in diabetes, blood pressure or decrease in adipose tissue.

The studies evaluating exercise regimens and its effects on kidney function in CKD patients have been conflicting. Largely due the variety of patients enrolled to the studies from those with baseline CKD and those without and others with confounding factors such as CVD and age. In addition, many of the studies are small with short follow up time thus affecting the chances of detecting a possible difference.

A study of 30 non-diabetic CKD patients randomized to cycling for 30 min versus maintenance of lifestyle saw no change in the rate of eGFR loss at 20 month follow up (Eidemak et al. 1997). One systematic review found ten studies looking at aerobic exercise effects on eGFR as an endpoint kidney parameter and meta-analysed nine of the RCTs comparing aerobic exercise with standard care for 151 and 154 patients respectively over mean period of 35 weeks and found an improvement in eGFR of 2.16 mL/min per 1.73m^2 (95% CI 0.18–4.13) however there was no significant within-group changes in eGFR (Wyngaert et al. 2018). Overall, the study also found an improvement in VO_2 peak (2.39 mL/kg/min) and decreased BMI (−0.72 kg/m^2) when compared to standard of care. The authors did further sensitivity analyses and separated studies with an elderly population and saw an improved eGFR of 3.43 mL/min/1.73m^2 (95% CI 1.62–5.23) with a decrease in heterogeneity score from $I^2 = 50\%$ to less than 25%. A prospective cohort study with 256 CKD stage III – IV patients had a median follow up of 3.7 years (Robinson-Cohen et al. 2014). A self-reported questionnaire was given and patients with >150 min of physical activity per week had the lowest rate of eGFR loss, −6.2% per year compared to −9.6% in inactive patients. This difference persisted after adjustment for sociodemographic factors and prevalent diseases. Unadjusted comparison for incidence of ESRD was higher in the inactive group, 5.7 vs 3.6 events per 100 person-years; however, when adjusted in 3 different models, exercise was not associated anymore.

In the absence of higher quality larger studies with long term data, the current evidence would suggest that exercise is likely beneficial and not harmful to patients with CKD. And if not a direct benefit for delaying kidney progression, it may help to reduce some of the other microvascular complications.

4.2.3 Weight Reduction (Decrease in Proteinuria)

The prevalence of obesity has increased over the last decades and it contributes to increased incidences of insulin resistance, type 2 diabetes, cardiovascular disease (CVD) and even CKD. In relation to CKD, obesity has been associated with the over activity of the renin angiotensin system, increased glomerular pressure, mesangial cell proliferation and endothelial wall dysfunction. Hormones leptin and adiponectin are produced by adipose tissue and their increased plasma levels also contribute to this progression through glomerulosclerosis and albuminuria respectively (Abou-Mrad et al. 2013).

In one systematic review with 522 patients, studies with dietary restriction weight loss decreased proteinuria by 1.7 g/24 h, representing a 55% decrease from baseline (Afshinnia et al. 2010). In patients who had microalbuminuria, all weight loss interventions decreased urinary albumin excretion. The study concluded that weight loss was associated with decreased proteinuria and microalbuminuria though studies were not long enough to see if any effects on CKD progression would occur. Another meta-analysis with 13 different studies found a mean decrease in proteinuria by 1.31 g/24 h from baseline mean of 2.5 g/24 h (Navaneethan et al. 2009). In this study however, no change in GFR or creatinine clearance was observed.

Bariatric surgery is an extreme form of weight loss and has demonstrated improvements in albuminuria where median urinary albumin to creatinine ratio dropped from 66 to 13 mg/g in one study (Ahmed and Byrne 2010).

Intentional weight loss can improve various cardiovascular outcomes and in relation to kidney disease can improve albuminuria and proteinuria in patients with mild to moderate CKD. There still needs to be more long term studies to analyze the impact on delaying progression to end stage renal disease.

4.2.4 Obstructive Sleep Apnea Management

Obstructive sleep apnea (OSA) was first identified as being correlated with proteinuria in the late 1980s.

It is hypothesized that the intermittent hypoxia may stimulate formation of reactive oxygen species that may promote inflammation and systemic endothelial dysfunction (Turek et al. 2012). In relation to CKD, this hypoxia may give rise to sympathetic tone and activation of the renin-angiotensin system to increase intraglomerular pressure (Sakaguchi et al. 2011).

A recent meta-analysis with 18 studies including 7090 patients demonstrated a significant relationship between OSA and poorer renal function with a pooled odds risk of 1.77 (95% C.I: 1.37–2.29; $p < 0.001$). The relationship was consistent between patients with and without diabetes mellitus and the adverse renal outcomes were represented by albuminuria and lower eGFR. In one observational study, patients who were adherent to their continuous positive airway pressure (CPAP)

therapy had a slower decline in renal function compared to non-CPAP adherent patients (−7.7% vs −10%) (Tahrani et al. 2013). Unfortunately, this did not meet statistical significance and the disparity in CPAP compliance speaks to the reality in clinical practice where non-adherence to CPAP is high. Another retrospective study followed patients over a median of 2.3 years saw a decline in eGFR of −0.07 mL/min/1.73m^2/year compared to −3.15 mL/min/1.73m^2/year (p = 0.027) (Puckrin et al. 2015). CPAP use was also associated with significantly reduced levels of proteinuria.

The clinical relevance of treating OSA in relation to delaying renal disease progression has mostly been limited to small retrospective cohort studies. While it is conceivable how treatment may improve or delay renal disease, the exact impact is still unknown. Due to the inconvenience and poor adherence to CPAP therapy, pharmacists may aid in counseling patients of this additional potential benefit to patients.

4.3 Anemia

4.3.1 Definition and Prevalence in CKD

Anemia refers to an absolute reduction in the total number of circulating red blood cells (RBC) resulting in symptoms relating to a decrease in tissue oxygenation. In CKD patients, an anemia of chronic illness presents itself as a result in decreased RBC production. Morphologically, the anemia is considered a normochromic-normocytic type. The prevalence of anemia increases as kidney function declines and doubles as the eGFR decreases below 60 mL/min/1.73m^2. The exact number however is variable and dependent on the definition of anemia used. The World Health Organization defines anemia as hemoglobin (Hgb) <130 g/L in men and Hgb <120 g/L in women; and with that definition, the prevalence of anemia in CKD patients is approximately 20.8–42.6% (Akizawa et al. 2018). The prevalence is also affected by certain comorbidities such as diabetes, which results in 3 times more anemic patients at CKD stage 3 (El-Achkar et al. 2005).

4.3.2 Cause of Anemia in CKD

The erythropoietin system functions to provide adequate tissue oxygen delivery through a homeostasis of replacing lost erythrocytes and stimulating new production that is triggered by hypoxia. Hypoxia is recognized by the transcriptional factor hypoxia inducible factor (HIF) system. The downstream response results in production of a glycoprotein hormone named erythropoietin, it is produced in the kidneys and circulates to tissue receptors to stimulate erythropoiesis especially at the bone marrow (Jelkmann 2004). A second minor source of erythropoietin production is in

the liver; which can increase significantly in the absence of kidneys. When secreted, erythropoietin has a half-life of approximately 5–12 h and interacts with the erythropoietin receptor resulting in a signal transduction cascade of cell division, preventing apoptosis and maturation of erythroid progenitors in the bone marrow.

In patients with CKD, there are many causes of anemia including inadequate erythropoietin production, iron, folate and/or vitamin B12 deficiency, erythropoiesis inhibition due to uremic toxins, inflammation, gastrointestinal blood loss, oxidative stress, inflammation, malnutrition and reduced red blood cell survival. In one study of hemodialysis patients, their mean red blood cell survival was only 73.2 ± 17.8 days (Ma et al. 2017).

In CKD patients, beyond the direct effects of kidney dysfunction on production of erythropoietin, iron deficiency occurs in ≥50% of non-dialysis dependent patients. Loss of iron is often a result of blood tests, surgical procedures, infection, systemic inflammation, impaired absorption secondary to elevated hepcidin concentrations and blood loss. Hepcidin is a circulating protein that promotes iron storage in the body and will decrease when iron deficiency is sensed (Ganz 2003). However, the protein is increased during inflammation as a protective mechanism to limit availability of iron to microorganisms that may be present during infection; and therefore, the protein is often increased as kidney function declines secondary to the overall inflammation in the body.

4.3.3 Clinical Impact and Complications in Patients and Therapeutic Goals

Anemia results in decreased carriage of oxygen to various organs and tissues in the body. As such, the resulting symptoms include headaches, fatigue, reduced mental acuity, syncope, palpitations, chest discomfort, shortness of breath and decreased exercise tolerance. These symptoms however are quite nonspecific and are similar to the symptoms described in patients with uremia and other causes as well.

Observational studies have demonstrated strong associations in dialysis patients for lowered Hgb levels and risk for death. One study saw a relative risk for death of 1.33 for patients with hematocrit levels less than 27% compared to those with 30–33% (Ma et al. 1999). Interestingly however, use of medication to target Hgb to normal concentrations of >130 g/L in the Choir trial resulted in a significant increase of the composite outcome driven by death and hospitalization (Singh et al. 2006).

Anemia may also indirectly cause cardiac injury due to the increased work from the heart in order to deliver oxygen to the tissues. When prolonged, this continuous strain may result in the development of left ventricular hypertrophy (LVH). Strong associations were demonstrated between worsening anemia and LVH in 78 hemodialysis patients where the lowest hemoglobin quartile patients had a mean left ventricular mass index 30% higher than the highest quartile (Silberberg et al. 1989). Similar to the mortality outcome, studies using medication to correct the anemia had no improvement or slowing of LVH either.

It is well described that anemia is an expected outcome from progressive worsening of kidney function but unfortunately the correction of said anemia has found no benefit with disease progression in a meta-analysis by Elliott et al. (2017)

A conversation with the patient about therapeutic goals and risks of anemia medications is necessary. With evidence that correction of anemia will not prevent or slow kidney function decline, nor improve cardiac function the goal should be to improve symptoms of anemia instead. Studies have shown that use of medication may improve patients' exercise tolerance, quality of life, fatigue symptoms and depressive symptoms (Canadian Erythropoietin Study Group 1990; Foley et al. 2000). Pharmacists may provide counseling when medications begin and help patients set forth realistic treatment plans to monitor improvements of said symptoms while balancing the appearance of any side effects from the medication.

4.3.4 Iron

Iron deficiency is evaluated by common iron tests for serum ferritin and transferrin saturation (TSAT). Ferritin is an intracellular storage of iron reflecting body's stores of iron and is an acute phase reactant that may increase independent of iron status in the presence of inflammation. TSAT is a measure of circulating iron as a calculation of free iron in serum divided by the storage protein transferrin delivering iron to the sites of use such as the bone marrow. In the general population and early CKD population, measurement of ferritin alone may be sufficient to evaluate the body's storage of iron, however as kidney disease progresses, the likelihood of inflammation, buildup of toxins and other factors begin to affect the reliability of ferritin and TSAT is needed as well for a more thorough approach for evaluation. Even with use of both tests however, one study evaluated the diagnostic utility of the two in non-dialysis patients and found a TSAT<20% has a sensitivity of 50% and specificity of 83% for predicting response to IV iron and ferritin <100 ng/mL is 48% and 90% respectively (Stancu et al. 2010). Therefore, when using these tests, the overall trends and history would be most useful when deciding to start treatment.

There is a wide selection of oral and intravenous iron available. Oral agents with different forms of iron salts such as iron gluconate, iron sulphate and iron fumarate are widely available and often without the need of a prescription as well. There is also the most experience with them in regards to safety and efficacy. Gastrointestinal adverse effects including nausea and constipation are the most common and may lead to reduced therapy compliance. The amount of elemental iron in the different iron salts varies with 12% in iron gluconate, 20% in iron sulphate and 33% in iron fumarate (Ponka et al. 2007). Iron is best absorbed on an empty stomach and may be affected by medications such as proton pump inhibitors, levodopa and levothyroxine. Decreasing the dose and increasing frequency or taking it with food acknowledging that less of the medication is absorbed may improve compliance by decreasing gastrointestinal side effects.

New preparations of iron supplement including ferric citrate and polysaccharide iron complex use the non-ferrous form to decrease gastrointestinal side effects. Ferric citrate was developed as a non-calcium based phosphate binder but clinical studies showed that iron was being absorbed as indicated by increases in ferritin and transferrin saturation levels even in hemodialysis patients (Fishbane et al. 2017; Lewis et al. 2015). Polysaccharide iron complex have improved absorption and tolerability profile compared to iron salts however they are significantly more expensive and has not demonstrated clinical superiority to the iron salts.

Parenteral iron has several formulations available with the first being iron dextran then ferric gluconate and iron sucrose. Iron dextran was first formulated as a high molecular weight iron dextran (HMW-ID) and was associated with rare but serious allergic reactions that could lead to anaphylaxis. The formulation was changed and is currently distributed as a low molecular weight iron dextran (LMW-ID) that is less variable and less immunogenic than HMW-ID. One of the largest comparative study using the US Medicare cohort with 688,000 patients, concluded that anaphylaxis was more likely with iron dextran than iron sucrose (Wang et al. 2015). Unfortunately, the study did not differentiate HMW-ID and LMW-ID, which we know can attribute for the differences in adverse events seen. The study also defined use of diphenhydramine and epinephrine as surrogates for anaphylaxis but these medications could have been used as premedication or as an unnecessary intervention and not a true response to the iron medication. Currently, a test dose of 25 mg of LMW-ID is given to a patient first and then observed for 10–15 min. If there are no adverse events, the remainder of the medication may be infused and no test dose is required again subsequently.

Ferric gluconate and iron sucrose are also available and in retrospective observational studies, these compounds have often been found to have less serious adverse events and sensitivities than iron dextran (both HMW-ID and LMW-ID) (Michael et al. 2002). Their smaller carbohydrate core however binds iron less tightly resulting in more free iron released after administration and therefore prevents large doses administered at once and multiple injections are required to deliver a complete replacement dose. When doses of more than 300 mg of iron sucrose was given in one study, a significantly higher incidence of reactions including myalgia, flushing, diarrhea, swelling of hands and feet and hypotension was observed (Chandler et al. 2001).

Ferumoxytol was engineered as a MRI contrast agent as an iron oxide compound linked to a polyglucose sorbitol carboxymethylether, but seeing that it can be used as iron supplementation it was then changed to be marketed for the CKD population. The advantage of this medication was its rapid bolus injection of 510 mg in 17 s that allowed clinicians to administer the medication during a patients visit without having to schedule a separate day and time should parenteral iron be necessary. Within months of use however, a large number of hypersensitivity reactions were reported and a black box warning changing the labeling from 17 s to an infusion rate of 15 min was necessary. In Canada, the product labeling was revised to add that the medication is contraindicated in any patients with any known history of drug allergy and in elderly patients >65 years of age. The uptake soon slowed down and the company Takeda withdrew the medication subsequently.

Ferric carboxymaltose (FCM) has been available since 2007 in Europe and 2009 in the United States. With its carbohydrate shell protecting the labile free iron, a 1 g dose can be administered as a 15-min intravenous infusion. FAIR-HF was the first study to observe a benefit in the medication in improving quality of life and in 6 min walking distances among patients with heart failure and iron deficiency with or without anemia (Anker et al. 2009; Ponikowski et al. 2015). A larger follow up study (CONFIRM-HF) extended to 12 months and the treatment effect was sustained with improvements in NYHA class, decreased risk of hospitalization for worsening heart failure, patient global assessment, quality of life and fatigue score in patients treated with FCM with statistical significance compared to placebo starting from week 24 and onwards (Ponikowski et al. 2015). The European Society of Cardiology Heart Failure guidelines were updated in 2016 with a strong recommendation for intravenous FCM to treat any chronic heart failure patients with iron deficiency.

Pharmacists are best suited to discuss with patients all the different iron supplements that are available. Almost all oral supplements do not require prescription and with proper counseling patients may understand their therapy better to ensure compliance. Even when choosing a parenteral option, understanding the different elements of each medication can help to individualize and tailor the medication best suited to the needs of the patient.

4.3.5 Erythropoiesis Stimulating Agents

Erythropoietin is a hormone secreted by renal interstitial cells to stimulate production of red blood cells in bone marrow as a response to decreasing oxygen levels in tissues. Other than tissue oxygen homeostasis the hormone has other non-erythropoietic effects at organs including the brain, blood vessels, liver and heart. It can induce vasoconstriction, causing an increase in arterial blood pressure and stimulate angiogenesis and cell regeneration in organs such as kidney, heart and central nervous system in experimental conditions. The first recombinant human erythropoietin first became available in the 1980s and prior to it anemia caused by renal failure was treated by frequent blood transfusions. This was associated with a high risk of transfusion-induced iron overload, infectious complications and antibody sensitization.

Epoetin alpha and epoetin beta were first obtained from recombinant DNA technology harvested from Chinese hamster ovary cells with a carbohydrate portion that is slightly different between the two forms. The medication is short acting with a half-life of approximately 8 h and frequent administration either twice or three times a week is necessary to maintain adequate hemoglobin levels.

Darbepoetin alpha was engineered through the addition of two N-linked oligosaccharide chains resulting in a three-fold increase to half-life, increased biologic activity and decreased receptor affinity (Egrie and Browne 2001). These changes allow for administration of the drug every week or every 2 weeks. Based on the peptide mass, 1 mg of darbepoetin alfa is equal to 200 units of epoetin though the

clinical equivalence may not be exactly the same (Locatelli et al. 2004). Head to head studies have not shown any difference in either darbepoetin or epoetin efficacy and the only benefit seen with darbepoetin is the convenient dosing interval that may be translated to improved compliance in an outpatient setting.

Methoxy polyethylene glycol-epoetin beta was created with further addition of glucidic residues and sialic acid molecules. This medication has a half-life of 135–139 h and can be administered every 2 weeks or once a month. Fifteen micrograms of the medication corresponds to about 1000 IU of epoetin alpha or beta (Cernaro et al. 2019).

Since the European patent for erythropoietin expired, several biosimilar epoetins have begun appearing on the market with the first epoetin biosimilar approved since 2007. Compounds epoetin alfa (HX575) and epoetin zeta (SB309) are both biosimilars of epoetin alpha (Goldsmith et al. 2018). They are marketed under different brand names depending on country. With use for 10 years in Europe, the retrospective safety data has shown that they are effective and well tolerated options with no unexpected harmful signals thus far. In all published studies, no neutralizing anti-erythropoietin antibodies have developed. An observational study of 8161 CKD patients showed no difference in reference medication and biosimilars in all-cause mortality, need for blood transfusion, major cardiovascular events or blood dyscrasias (Trotta et al. 2017).

All medications can be administered intravenously or subcutaneously. With the wide spread use of ESAs the side effects are well documented in literature. The Normal Hematocrit Cardiac Trial (NHCT) saw increased vascular access thrombosis and a trend towards death and heart attacks in the higher hematocrit arm (Besarab et al. 1998). This outcome was further demonstrated by the CHOIR study that saw an increased risk for the composite outcome including death and cardiovascular events in CKD non-dialysis patients treated towards the higher hemoglobin target requiring the study to be stopped early (Singh et al. 2006). A similar study CREATE was published in the same year and did not see any differences for cardiovascular events but a pre-specified secondary analysis did show a higher risk of end-stage renal disease requiring dialysis in the higher target group. The most recent study TREAT did not see a difference in the primary composite outcome of death or CV event but did see a significant increase in incidence of stroke in the higher hemoglobin target group. Other notable side effects to this group of medications include symptoms of headaches, dizziness, nausea, high blood pressure, increased thrombosis risk, pain at injection site and swelling with most of these side effects increasing proportionately as target hemoglobin and amount of medication used rises. A more rare side effect is the incidence of pure red cell aplasia (PRCA) a condition where the bone marrow stops making red blood cells causing anemia that affects red blood cells only and not white blood cells. In the mid-1990s, there was several case reports of an antibody mediated form of pure red cell aplasia (PRCA) associated with ESA therapy. It was traced back to a change in stabilizing agent of the product from human serum albumin to polysorbate 80 and glycine that may have interacted with the uncoated rubber stoppers of prefilled syringes to increase the immunogenicity of

the medication (McKoy et al. 2008). By 2003, the company replaced the uncoated rubber stoppers with Teflon stoppers and improved cold chain storage management and the incidence of PRCA went back to historic lows (Macdougall et al. 2012). There continues to be small cases reported worldwide almost all associated with subcutaneous injection of the medication and even some reports following use of epoetin biosimilars (Macdougall et al. 2012).

4.3.6 Hypoxia-Inducible Factor Prolyl-4-Hydroxylase Inhibitors (HIF-PHIs)

The hypoxia inducible factor system functions as 2 proteins HIF-α and HIF- β. When sufficient oxygen is present, HIF-α is hydroxylated for degradation by HIF-prolyl hydroxylases which requires oxygen as a co-substrate. After hydroxylation, HIF-α is targeted by the von Hippel-Lindau protein to be destroyed. HIF-β is not affected by presence of oxygen for degradation.

When the body is in a state of hypoxia, HIF-α will begin to accumulate to form a heterodimer with HIF-β leading to downstream increased erythropoietin production. New research into HIF stabilizers to reduce the degradation of HIF-α has been under investigation in recent years. There are approximately 7 drugs registered on clinicaltrials.gov undergoing investigation with 3 of them undergoing Phase 3 studies.

Roxadustat (FG-4592), an oral medication, is one of the medications currently undergoing Phase 3 studies. In their phase 2a study studying anemic CKD patients, the medication showed increases in erythropoietin and hemoglobin levels as well as a reduction in hepcidin concentrations with 0.7 to 2.0 mg/kg given 2 or 3 times per week compared to controls within 4 weeks of treatment with no adverse events observed. Roxadustat was then studied in hemodialysis and peritoneal dialysis patients and raised hemoglobin by 20 g/L in 7 weeks of treatment with 4.3 mg/kg weekly for 12 weeks. The current phase 3 studies will continue to evaluate Roxadustat compared to epoetin alpha (NCT02174731) and epoetin alpha or darbepoetin alpha (NCT02278341) in CKD patients on dialysis.

Vadadustat (AKB-6548), also an oral medication, has been studied in placebo controlled phase 2 studies in CKD 3a to 5 patients. Fifty four percent of patients on vadadustat met the primary endpoint of achieving a hemoglobin level of 110 g/L or more or a mean increase in hemoglobin by 12 g/L compared to 10.3% in the control group (NCT01906489). Adverse events were similar in the two groups during the 20-week study. Two phase 3 studies are currently recruiting patients to evaluate the effects compared to darbepoetin alpha in CKD non-dialysis (NCT02680574) and dialysis dependent patients (NCT02892149).

Daprodustat (GSK1278863) is another oral medication undergoing phase 3 studies currently studying the medication compared to darbepoetin alpha in CKD non-dialysis patients (ASCEND-ND study; NCT02876835).

This group of HIF stabilizing compounds will be a new and significant addition to our armamentarium for treating anemia in CKD patients. This new class of medication and their convenient dosage form as an oral medication given once a day or three times a week will certainly be a preferred agent prior to going to the injectable ESA medications. There may even be a role for this medication for use in other conditions affecting RBC production.

4.3.7 Treatment

The initial evaluation of a patient suspected of anemia requires a thorough history and physical examination along with blood tests and ruling out other possible culprits such as hemolysis or bleeding. In patients with CKD, other than the usual blood tests for complete blood cell count with red blood cell indexes, reticulocyte count, and vitamin B12, a thorough iron panel with serum ferritin, and transferrin saturation would be informative as well since most CKD patients are iron deficient as a cause for their anemia.

When evaluating patients for iron deficiency in non-dialysis dependent CKD patients, treatment is recommended when ferritin <100 ng/mL or TSAT <15% and in hemodialysis patients when ferritin <300 ng/mL or TSAT <20%. These levels are used loosely and the trends are more important as different guidelines will often have slight differences in the exact numbers. For non-dialysis dependent CKD patients, oral iron medications are often started first due to convenience, as intravenous iron requires a visit to a medical facility for the medication to be administered. A recent meta-analysis included 2369 CKD patients and 818 hemodialysis patients concluded that intravenous iron patients were more likely to reach a hemoglobin response greater than 10 g/L; however, intravenous iron had a higher risk of hypotension (risk ratio 3.71) with fewer gastrointestinal side effects (risk ratio 0.43) (Shepshelovich et al. 2016). When comparing side effects, oral iron had more constipation side effects but parenteral iron had more serious adverse events. Therefore, for safety and convenience reasons, oral iron should be tried first and parenteral iron be used if there is an inadequate response or patient cannot tolerate oral therapy in non-dialysis patients.

When deciding to start ESAs for anemia, the goal of therapy should be first reviewed with the patient. As clinical trials have not found any significant clinical benefit to restoring hemoglobin levels to normal, the goal of treating iron-replete patients are to improve quality of life and decrease the need for transfusion while minimizing any potential adverse events with use of these medications. The ideal hemoglobin range and target has been a moving number over the last decade and the center of many studies; with each revision, the target has decreased with more evidence of the potential harms of the medication. The most recent international KDIGO guidelines have recommended to start the conversation for use of ESAs when the hemoglobin is <100 g/L in CKD non-dialysis patients and when it is started for the hemoglobin to not rise above 115 g/L (KDIGO 2012). In dialysis patients, ESA therapy is used to prevent the hemoglobin from falling below 90 g/L

and recommended to be started when hemoglobin is between 90 and 100 g/L and again to avoid raising the hemoglobin target to above 115 g/L.

After initiating treatment, pharmacists may play an active role in monitoring the hemoglobin; it should be measured minimally every 2 weeks with the expectation of approximately 10 g/L increase in hemoglobin within the first month of treatment. If the hemoglobin increases by more than 10 g/L in the first 2 weeks, the ESA dose should be reduced by 25–50% to prevent any adverse events. The potential risks with using ESAs as described above should be discussed with the patient and individualization of hemoglobin target can be based on patient lifestyles. For example, a sedentary patient may be comfortable at a hemoglobin of 95 g/L but a younger active patient may require a hemoglobin closer to 110 g/L to be able to continue their daily activities. As a patient continues on ESA therapy, iron stores should be rechecked at least every 3 months in dialysis patients and every 6 months in non-dialysis patients as iron deficiency can be induced with erythropoiesis. The dose of the ESA should also be re-evaluated with hemoglobin checks at least every 6 months in non-dialysis patients and at least every 3 months in dialysis patients. During these times, the pharmacist may also evaluate the effectiveness of the dose and hemoglobin target by asking about anemia symptoms and check for any side effects such as headaches, high blood pressure, symptoms of heart failure or swelling.

4.4 Mineral Bone Disease

4.4.1 Definition and Prevalence in CKD

Chronic kidney disease mineral and bone disorder (CKD-MBD) is a systemic disorder manifested by either one or a combination of three findings: (i) laboratory abnormalities manifested in serum calcium (Ca), phosphorous (PO4), parathyroid hormone (PTH) or vitamin D; (ii) abnormalities in bone turnover, mineralization, volume, linear growth or strength; (iii) vascular or soft tissue calcification. These surrogate markers either individually or together results in clinical outcomes of fractures, cardiovascular disease and/or mortality in CKD patients. A study by Levin et al. attempted to quantify the prevalence of this abnormality with 1814 patients of different eGFR levels and found that patients began experiencing laboratory abnormalities at eGFR 40 mL/min/1.73m^2 and continues to rise in a linear fashion as kidney function declines.

4.4.2 Cause of MBD

As kidney function declines, a complex struggle to maintain calcium, phosphate, and parathyroid hormone (PTH) homeostasis ensues. In early kidney disease, disruption and elevation in fibroblast growth factor 23 (FGF-23), a phosphaturic hormone, is one of the first markers of disrupted mineral metabolism. This hormone is

released as phosphate elimination is affected by impaired renal function to inhibit renal tubular phosphate reabsorption and also reduce systemic levels of calcitriol to decrease gastrointestinal tract PO4 absorption. (Diniz and Frazão 2013) The progressive FGF23 rise over the course of CKD is eventually insufficient to compensate for the declining functional nephrons resulting in a persistent hyperphosphatemia (Hruska et al. 2017). At this point, the effect of FGF-23 has not only affected PO4 but it also inhibits 1-alpha-hydroxylase to decrease calcitriol production and stimulates 24-hydroxylase to breakdown the vitamin D molecule creating a downstream hypocalcemia (Shimada et al. 2004; Prié and Friedlander 2010). The hypocalcemia is sensed by the parathyroid gland resulting in parathyroid hormone (PTH) secretion that leads to a secondary hyperparathyroidism. Parathyroid hormone causes bone resorption to increase plasma calcium levels but releases PO4 at the same time to further worsen hyperphosphatemia causing a cyclic positive feedback for FGF-23 to rise in response again. The hyperphosphatemia may also worsen the hypocalcemia by precipitating together to form crystals in body tissues and blood vessels. The parathyroid cells sensing this continuous hypocalcemia will continue secreting PTH causing a nodular hyperplasia that may eventually be nonresponsive to a normalized calcium level producing a tertiary hyperparathyroidism. When this state is reached, one treatment option is through surgery whereby a portion of the parathyroid gland is removed completely.

The impact of elevated PTH and uremic toxin accumulation as kidney function declines creates an abnormal bone histology that collectively is known as renal osteodystrophy. It is quantified by a classification system with three components represented by bone turnover, mineralization and bone volume. In patients with over production of PTH, a high turnover of bone may result in osteitis fibrosa where a softening of the bone occurs. Overtreatment may result in the opposite effect for a low turnover bone disorder termed adynamic bone disease. Protein bound uremic toxins and overuse of medications such as aluminum may also contribute to another type of bone disorder affecting mineralization termed osteomalacia. In this bone, the collagen cross-linkages incorporate toxins or medications in disarray resulting in weakened mechanical bone properties (Hou et al. 2018). Overall, these bone abnormalities may occur independently of detectable laboratory markers and thus is another component of CKD-MBD.

Vascular calcification is inappropriate pathological deposition of mineral in the form of calcium phosphate salts in vascular tissues. In CKD-MBD, vascular calcification is characterized by intimal and medial calcification. Intimal calcification is similar to atherosclerotic plaque and is produced by osteoblastic transition of cells in neointima. This plaque like calcification is unstable and capable of rupturing causing thrombus formation and occlusive disease affecting coronary perfusion. Medial calcification is linked to vascular smooth muscle cells undergoing chondro-osseous transition and is the exclusive form observed in pediatric CKD patients. While abnormal calcium and PO4 levels play a large role in CKD calcification this process is augmented by the elevations in FGF-23 and PTH hormones as well to affect vascular smooth muscle cells resulting in these intimal and medial effects.

4.4.3 Clinical Impact and Complications in Patients and Therapeutic Goals

As complex as the different elements of CKD-MBD are, the complications associated with the abnormalities are numerous as well. As renal function declines, hyperphosphatemia has been associated with symptoms of pruritus but recent studies have shown that changes in calcium, ferritin and even PTH levels from norm can be associated with increased burden of pruritus. Given the inconsistency, it is best to ask the patient whether the symptom exists and if it does, may counsel the patient that normalization of these parameters may improve pruritus symptoms but may not eliminate it completely.

The direct inhibition of vitamin D activation by FGF-23 will eventually lead to the downstream effects of hypocalcemia. Though the body attempts to restore this homeostasis through PTH release, the symptoms of hypocalcemia and vitamin D deficiency may still be present in the patient. Symptoms of hypocalcemia include paresthesias, muscle cramping and spasms. The constant release of PTH and subsequent effects on bone may appear as bone and joint pain to the patient but the constant release and effects on the bone will result in pathological changes unknown to the patient until a fracture occurs. Studies have shown an increase risk of fracture by 1.5–3 times in CKD non-dialysis patients compared to patients without CKD and increasing to 4–14 times in hemodialysis patients. In addition to the fracture itself, it also has downstream effects of inactivity, hospitalization and mortality for the patient.

Elevated levels of PTH, calcium, and phosphate have all been independently associated with a high risk of death and cardiovascular events. The aforementioned rise in FGF-23 has been associated with cardiovascular risk in CKD as a direct pathogenic factor causing left ventricular hypertrophy through activation of the calcineurin-NFAT pathway in cardiac myocytes (Faul et al. 2011). Vascular calcification results in vascular stiffness, increases in systolic blood pressure, and left ventricular hypertrophy that are all contributors for the high cardiovascular risk and cardiac mortality in CKD patients (Hruska et al. 2017). Calcifications have also been reported in soft tissue areas including eyes, joints and visceral organs. A rare but limb threatening disorder termed calcific uremic arteriolopathy or calciphylaxis may occur in CKD patients. It is characterized by medial wall calcification and intimal hyperplasia presenting as chronic, painful non-healing wounds. The imbalance in mineral content is the most common risk factor with calciphylaxis and the vascular calcification started by a trigger event such as trauma or surgery is what is believed to be the cause of this condition.

For pharmacists, it is important to understand the different symptoms that patients may present with in relation to CKD-MBD. The therapeutic goals are aimed towards normalizing biochemical markers towards normal values; it is possible however that certain symptoms and progression may not be entirely preventable even with normalization but is a modifiable risk factor that we should aim towards. With early detection and monitoring, we also hope to prevent or

slow the progression of renal osteodystrophy such as impaired bone density or fractures, preventing extraskeletal calcifications and preventing need for parathyroidectomy.

4.4.4 Phosphate Binders

Various therapies have been developed aiming to modify the different components of CKD-MBD. The earliest treatments aimed to normalize serum PO4 levels and since 70–80% of PO4 is absorbed from food intake the target was to decrease the amount of PO4 available for absorption. Patients are first counseled to limit the amount of phosphate from food sources but even with the strictest diet, the overall phosphate burden will still rise as PTH hormone begins to breakdown bone with CKD progression. All of the medications rely on binding to PO4 in foods therefore patients should be counseled to take them before eating or with the first bite of the food.

4.4.4.1 Calcium Based Phosphate Binder

Calcium-based binders have historically been the safest and most economical option as the medications are readily available and effective in binding to the phosphate in foods. Calcium salts such as calcium carbonate and calcium acetate have been used for decades; however, an increased signal for risk of hypercalcemia and possible contribution to vascular calcification has been observed in patients receiving these drugs recently (Locatelli 2014). If used, calcium acetate may achieve a similar level of phosphate binding to calcium carbonate but at a lower elemental calcium burden (Ben Hamida et al. 1993), though recent studies have shown the risk of calcification appears to be similar with both salts (Navaneethan et al. 2011). The efficacy of calcium carbonate is dependent on gastric pH as it requires an acidic environment to dissolve but needs a higher pH to bind phosphate effectively (Bellinghieri et al. 2007). Calcium carbonate is available in various dosage forms including chewable and non-chewable tablets, and even liquid allowing for more routes of administration including enteral tubes if necessary. On average the daily calcium carbonate dosage is approximately 1–3 g equating to approximately 2–6 tablets. If using calcium acetate there is only the tablet available and the average daily dose would equate to approximately 3–12 tablets. The most common side effects are gastrointestinal related particularly constipation with use of calcium carbonate and diarrhea with calcium acetate. Calcium may affect the bioavailability of other drugs as well including levothyroxine and tetracyclines and the potential hypercalcemia may enhance cardiac effects of digoxin leading to arrhythmias.

4.4.4.2 Non-calcium Based Binders

Aluminum salts were the main binders used in the 1980s but the association with toxic effects such as osteomalacia, microcytic anemia and dementia has resulted in it falling out of favor for safer alternatives (Savory et al. 1985). When ingested, 0.01% of the dose is systemically absorbed thus in countries where it is still used, as the medication is an effective and cheap binder, levels need to be monitored regularly to ensure it does not rise above 1.5 umol/L. (Mudge et al. 2011) On average, the daily dosage is approximately 2–10 g equating to 4–20 capsules.

Magnesium based binders are another effective phosphate binder but toxic effects were seen when absorption of magnesium rose serum levels rise above 1.05 mmol/L causing symptoms of respiratory depression and cardiac arrest. In dialysis patients, where magnesium is found in the dialysate, symptoms such as pruritus, altered nerve conduction and parathyroid gland dysfunction were described in some studies where magnesium was used as a binder. Again, due to safety and availability of alternative options, it is used less commonly as monotherapy but some new medications do have it in combination with calcium acetate approved for dialysis patients. As a monotherapy binder, the average daily dose is 200–600 mg daily equating to approximately 3–9 tablets.

Lanthanum carbonate is a salt with earth metal lanthanum in a trivalent cation that binds phosphate optimally at pH 3–5 (Autissier et al. 2007). It is absorbed minimally and 99% of the dose is excreted through bile and feces. The tablets can be crushed and different dosage strengths have different sizes for ease of administration. Overall, the medication in comparison to calcium has a higher incidence of nausea but significantly less constipation adverse events. One study found an overall mortality benefit in patients over 65 years treated with lanthanum after 2 years compared to patients on calcium binder therapy (Wilson et al. 2009). There are some signals of tissue deposition of lanthanum in dialysis patients and kinetic modeling suggests that lanthanum concentrations in bone tissue may increase sevenfold after 10 years of treatment with clearance of 13% per year after stopping treatment (Bronner et al. 2008). In one long-term human study, no significant adverse effects on bone, liver or nervous system was observed but follow up data was only available for 36 patients beyond 4 years of treatment (Hutchison et al. 2008). Lanthanum will interact with ciprofloxacin to reduce its bioavailability by 50% and may affect absorption of tetracyclines as well. The average daily dosage is 1.5–3 g equating to approximately 2–3 tablets (How et al. 2007).

Sevelamer hydrochloride acts as an anion exchange resin to bind phosphate and exchange it for chloride ions in the gastrointestinal tract. It is a non-specific anion exchange resin however and binds bile acids and low-density lipoprotein cholesterol as well (Evenepoel et al. 2009). Sevelamer has been shown to reduce the bioavailability of ciprofloxacin by approximately 50% and may potentially reduce levels of mycophenolate mofetil and cyclosporine (Pieper et al. 2004; Kays et al. 2003). Compared to calcium, there is a higher incidence of nausea and abdominal

pain and is contraindicated in patients with bowel obstruction with caution in patients with dysphagia, and gastrointestinal motility disorders. The medication cannot be crushed or chewed and the average daily dose is 2.4–12 g equating to 3–15 tablets daily.

4.4.4.3 Iron Based Binders

A relatively new category termed iron based binders has two medications on market: ferric citrate hydrate and sucroferric oxyhydroxide.

Sucroferric oxyhydroxide has been approved since 2013 in the US and since 2014 in the EU for treatment of hyperphosphatemia in dialysis patients. It has two mechanisms to bind to phosphate where the first relies on low pH values for the precipitation of iron phosphate to be formed and phosphate adsorption to the iron complex in the intestinal lumen both leading to excretion of phosphate in the feces. It is a chewable tablet with 500 mg of iron that is partially water-soluble. In phase II studies, patients were taking on average 3 tablets a day with lower drop-out rates compared to the sevelamer group requiring eight tablets for similar phosphate targets (NCT01324128). The extension phase III study continued to see reduced phosphate levels with no evidence of iron accumulation (NCT01464190). Though iron release is meant to be minimal, studies have shown a statistically significant increase in mean TSAT (+4.6 vs 0.6%) and hemoglobin levels (+1.6 vs−1.1 g/L) in the sucroferric oxyhydroxide group versus the sevelamer group (Covic et al. 2017).

Ferric citrate is currently approved in Japan and since 2014 in the US for treatment of hyperphosphatemia in CKD patients. Similar to sucroferric oxyhydroxide, studies have seen similar phosphate lowering efficacy as sevelamer with significant increases to ferritin and TSAT values. In a placebo controlled study, 52.1% in ferric citrate group compared to 19.1% in placebo group had an increase in hemoglobin of >10 g/L. (Fishbane et al. 2017)

The convenience and decreased pill burden of this group of binders could be quite favorable for anemic non-dialysis CKD patients. If not for the decreased need for additional iron tablets, this group of binders required less tablets overall compared to sevelamer in clinical studies to achieve similar phosphate binding. Gastrointestinal side effects were the most common with diarrhea and discoloured stools. There are currently some other formulations undergoing clinical trials such as iron-magnesium hydroxycarbonate (SBR759). Drug interaction studies thus far have only listed levothyroxine.

4.4.4.4 Vitamin D

Another target for the treatment of CKD-MBD involves addressing vitamin D deficiency. The major circulating form of vitamin D is the 25-hydroxyvitamin D (25[OH]D) which requires further hydroxylation in the kidney to become the bio-

logically active 1,25-hydroxyvitamin D (1,25$[OH]_2$D). Epidemiological studies have shown that >80% of CKD patients have low serum 25(OH)D levels (Ngai 2014). The main causes and risk factors include age, gender, adiposity, diabetes mellitus, reduced skin synthesis of vitamin D, low physical activity and impaired 25(OH)D tubular reabsorption. In response, the first line of therapy would be to administer oral vitamin D supplementation. Ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) are two readily available oral preparations over the counter. Ergocalciferol is a plant-based derivative and cholecalciferol is made from irradiation of 7-dehydrocholesterol from lanolin and chemical conversion of cholesterol. Kinetic studies have shown that ergocalciferol is less potent with a shorter duration of action than cholecalciferol (Armas et al. 2004). When compensating for the kinetic differences of the two medications, both are equally effective in raising serum 25(OH)D levels. Given that vitamin D is fat soluble, different dosing strategies of daily, weekly or monthly are feasible to restore 25(OH)D levels. Vitamin D toxicities are uncommon but would be exhibited by hypercalcemia with extraosseous calcification or hypercalciuria.

Unfortunately, with decreasing renal function and rising FGF-23 levels, exogenous supplementation of vitamin D will eventually be insufficient as FGF-23 directly inhibits the hydroxylation in the kidney to prevent activation to 1,25(OH)D. When this occurs, vitamin D receptor agonists will be necessary to ensure biological vitamin D activity. Two medications are currently available, a prehydroxylated prohormone 1(OH)D (alfacalcidol) and fully active calcitriol (1,25$[OH]_2$D). Alfacalcidol relies on the liver to hydroxylate the last position and is available as an oral capsule with various dosages. Calcitriol is available as an oral capsule and intravenous preparation but is significantly more expensive than alfacalcidol. Similar to vitamin D, these receptor agonists have the same adverse effects.

4.4.4.5 Calcimimetic

Treatment for high PTH levels were previously limited to two options, vitamin D receptor activators and surgical parathyroidectomy until the introduction of a new class of agents known as calcimimetics. This new group of medication allosterically increases the sensitivity of the calcium sensing receptors on the parathyroid gland to calcium to create the negative feedback necessary to decrease PTH release. Cinacalcet was the first in the group as an oral medication with mostly gastrointestinal side effects such as nausea and diarrhea. Hypocalcemia and hypophosphatemia is quite common as well when starting the medication but is due to the response of the bone in forming new bone to decrease the serum levels of the two minerals.

Etelcalcetide is a new intravenous calcimimetic that has recently become available. In one head to head RCT, the use of IV etelcalcetide in hemodialysis patients with PTH levels >500 pmol/L was not inferior to oral cinacalcet for achieving PTH reduction of >30% over 26 weeks and even reached superiority criteria with 68.2% of patients reaching PTH reduction >30% vs 57.7% in cinacalcet group ($p = 0.004$) (Block et al. 2017). Interestingly despite being given intravenously, the rates of gas-

trointestinal side effects were comparable between the two medications with 18% of etelcalcetide patients experiencing nausea and 22.6% in cinacalcet group and 13.3 and 13.8% for vomiting respectively. The medication is convenient in dialysis patients but the drug is still quite new and doesn't necessarily offer many drastic advantages over cinacalcet.

4.4.4.6 Treatment

The difficulty in treatment lies in the lack of consistent evidence of any interventional trials improving morbidity or mortality when treating CKD-MBD. Though epidemiological evidence suggests that lowering PO4 do confer benefits, the high tablet burden and adverse effects make it difficult for clinicians to know how aggressive to be. The updated 2017 KDIGO guidelines recommend using phosphate binding agents to lower elevated phosphate levels toward normal range while avoiding hypercalcemia and that treatment should be based on progressively or persistently elevated serum phosphate.

All phosphate binders are effective at reducing serum PO4 levels but the choice of which is often based on adverse events, tolerability, pill burden, cost, patient preference and other potential benefits with each individual medication. In the 2017 KDIGO update, the recommendations for use of calcium-based binders were changed to suggest restriction of use in patients with arterial calcification and/or adynamic bone disease and/or if serum PTH levels were persistently low. This change comes from 3 RCTs that have demonstrated the promotion of progressive vascular calcification with calcium-based binders and the ability for non-calcium based binders to potentially slow the progression and even reverse calcification in some studies (de Francisco et al. 2016; Block et al. 2012; Barreto et al. 2008; Di Iorio et al. 2013). In the updated Cochrane 2018 review with 104 RCTs and 13,744 patients, the updated conclusion supports the use of sevelamer compared to calcium-based binders in dialysis patients for decreased all cause death; however, this was only examined as part of the outcomes in three studies (Ruospo et al. 2018). The authors do note that it is uncertain whether this lowered death is a result of avoiding additional calcium from calcium-based binders or a direct beneficial effect of sevelamer or both. The Landmark trial is near reporting, and will address whether lanthanum may confer similar death or cardiovascular benefits like sevelamer. There is currently no study for iron-based binders on these outcomes yet. Furthermore, all of these studies are in dialysis patients and some done in a time where phosphate targets were much lower and significantly higher dosages of binders were used and thus the impact of phosphate binder on cardiovascular outcomes for non-dialysis CKD patients remains uncertain.

Similar to phosphate, the optimal PTH level is unknown as well; however, patients with progressively rising or persistently elevated levels should be evaluated for modifiable factors such as hyperphosphatemia, hypocalcemia, and vitamin D deficiency per KDIGO 2017 guidelines. Only patients with eGFR <15 mL/min on dialysis have a recommendation to keep the PTH levels between 2 to 9 times the

upper limit of normal for the assay. This recommendation comes from a 2-year observational study where patients below 2 and above 9 times the upper limit of normal had a significant rise in their all cause death hazard ratio (Kalantar-Zadeh and Fouque 2017). Though treatment of PTH, has not shown any reduction or improvement in outcomes such as hospitalizations, cardiovascular events, or survival, its reduction has shown benefits in bone abnormalities with statistically significant decreases in bone marrow fibrosis, bone remodeling rate and osteomalacia (Hamdy et al. 1995).

An appropriate approach would be to monitor patients' calcium, phosphate and PTH regularly (every 6–12 months) starting at CKD stage 3 (eGFR <60 mL/min) and if on repeated laboratory tests the phosphate or PTH levels are elevated, to start the discussion with the patient about the implications in care. Should there be no contraindications such as arterial calcification and/or persistently low PTH, calcium based binders are still an effective binder to start with. They are widely available and side effects are well described. Patients may start with calcium carbonate with their largest meal and follow ups can be done to monitor serum levels. As phosphate levels continue to rise with decreasing renal function, the dosage of the medication may need to be increased and alternative binders may need to be considered as side effects present as well. Eventually, there may come a point where medications may be insufficient and consideration for removal using a dialysis modality may need to be considered.

An integrated approach is needed in the treatment for CKD-MBD. It is an area of high pill burden and restrictive diets that do not readily translate to clinical outcomes readily seen. The focus is multidimensional with modifications to diet, medication and lifestyle. Pharmacists can aid in this through early recognition of symptoms, discussions with patients on choosing the most appropriate treatment and monitoring for modifiable risk factors.

4.5 Dyslipidemia and CKD

4.5.1 Introduction

Chronic kidney disease (CKD) patients are at an increased risk of cardiovascular morbidity and mortality. In the general population, dyslipidemia is a well-established risk factor of coronary artery disease. However, this has been less clear in the renal population due to a relative paucity of studies examining the effects of dyslipidemia treatment on clinical outcomes in CKD patients. Despite CKD being considered a coronary heart disease equivalent where statin therapy is indicated, many early lipid guidelines did not include recommendations on the best approach to the treatment of dyslipidemia in CKD (Wanner et al. 2005). However, following the publication of multiple landmark lipid trials in CKD patients, the Kidney Disease: Improving Global Outcomes (KDIGO) organization released a guideline in 2013 on lipid man-

agement in CKD (Wanner et al. 2005). Other major lipid guidelines including the Canadian and European ones have since been updated to include recommendations specifically for CKD patients (Anderson et al. 2016; Catapano et al. 2016). In this section, we will start by discussing the pathogenesis of dyslipidemia in CKD followed by a review of the recommendations from the KDIGO lipid guidelines. Similar recommendations have been provided in the Canadian and European lipid guidelines; therefore, they will not be discussed here.

4.5.2 Pathogenesis

There are distinctive differences in the lipid profiles of CKD patients compared to the general population. This includes quantitative as well as qualitative changes. Further differences are noted depending on the CKD stage, proteinuria level, and type of renal replacement therapy (see Table 4.3). CKD patients with nephrotic syndrome generally have the worst looking lipid profiles compared to the general population as well as other CKD patients without nephrotic syndrome or CKD stage five patients on hemodialysis (HD) or peritoneal dialysis (PD). They have considerably elevated total cholesterol, low-density lipoprotein cholesterol (LDL-C) and triglycerides, and relatively low high-density lipoprotein cholesterol (HDL-C) levels whereas the total cholesterol and LDL-C levels between CKD patients without nephrotic syndrome including those who are on dialysis and the general population are fairly similar. The differences lay mostly in the lower HDL-C and higher triglyceride levels in these patient populations (Weiner and Sarnak 2004; Kwan et al. 2007; Bermúdez-López et al. 2017; Mikolasevic et al. 2017).

Table 4.3 Trend of changes in lipids, lipoproteins, and apoA-IV in various stages of CKD

Parameter	CKD 1 to 5	Nephrotic Syndrome	Hemodialysis	Peritoneal Dialysis
Total cholesterol	↗	↑↑	↔↓	↑
LDL cholesterol	↗	↑↑	↔↓	↑
HDL cholesterol	↓	↓	↓	↓
Non-HDL cholesterol[a]	↗	↑↑	↔↓	↑
Triglyceride	↗	↑↑	↑	↑
Lipoprotein(a)	↗	↑↑	↑	↑↑
ApoA-I	↘	↗	↓	↓
ApoA-IV	↗	↑↘	↑	↑
ApoB	↗	↑↑	↔↓	↑

Reproduced with permission from Kwan et al. J Am Soc Nephrol 2007;18:1246–61 (Kwan et al. 2007)

Explanation of arrows: Normal (↔), increasing (↗), increased (↑), markedly increased (↑↑), decreasing (↘), and decreased (↓) compared to healthy patients

[a]Non-HDL cholesterol includes cholesterol in LDL, very-low-density lipoprotein, intermediate-density lipoprotein, and chylomicron and its remnant

Hypertriglyceridemia is seen from the earliest stages of CKD with the highest triglyceride levels being observed in patients with nephrotic syndrome and in those on PD. Hypertriglyceridemia results from an increase in the hepatic production of triglyceride-rich lipoproteins (very-low-density lipoproteins, chylomicrons and their remnants) and a decrease in their catabolic rate, which is a result of decreased activity of two lipases, hepatic triglyceride lipase and peripheral lipoprotein lipase, whose primary physiologic function is to cleave triglycerides into free fatty acids for energy production or storage. Prolonged exposure of the arterial wall to remnant lipoproteins may predispose to atherogenesis (Kwan et al. 2007; Bermúdez-López et al. 2017; Mikolasevic et al. 2017).

LDL-C levels vary depending on the stage of CKD. Early on, CKD patients, and especially those with nephrotic syndrome, tend to have elevated LDL-C levels due to an increase in the production of low-density lipoproteins (LDLs) and a decrease in LDL catabolism. However, in end-stage renal disease patients, and in particular in those on hemodialysis (HD), LDL-C levels may be normal or reduced because of a decrease in the production of LDLs, which offsets the reduction in LDL catabolism. Although LDL levels may be normal or reduced in patients with advanced CKD, they are smaller, denser and more atherogenic. CKD patients have impaired antioxidant defense mechanisms, which creates an oxidative environment where lipoproteins may undergo abnormal posttranslational modification of their components and subsequent altered biological function (Kwan et al. 2007; Bermúdez-López et al. 2017; Mikolasevic et al. 2017).

HDL-C levels are usually reduced in CKD patients due to a number of factors. The formation of high-density lipoproteins (HDLs) is decreased because of the reduced availability of its main components, i.e. apolipoprotein AI and AII. As well, the activity of lecithin-cholesterol acyltransferase (LCAT), which is an enzyme involved in the esterification of free cholesterol and subsequent synthesis of HDL, is impaired while the activity of cholesterol ester transfer protein (CETP), which supports the transfer of cholesterol esters from HDL to triglyceride-rich lipoproteins, is increased. The activity of paraoxonase, an HDL-associated enzyme that inhibits the oxidation of LDL and possibly HDL particles, is reduced. All of these factors together place CKD patients at higher risk of developing atherosclerotic complications (Kwan et al. 2007; Bermúdez-López et al. 2017; Mikolasevic et al. 2017).

4.5.3 KDIGO Guideline Recommendations

The KDIGO guidelines recommend that in adults with newly identified CKD including those on dialysis or who have received a kidney transplant that a lipid profile consisting of total cholesterol, LDL-C, HDL-C, and triglycerides be obtained for evaluation (grade 1C) (KDIGO Work Group 2013a). In the KDIGO guidelines, recommendations are graded according to the strength of the recommendation (Level 1 = we recommend, Level 2 = we suggest, or not graded) and the quality of supporting evidence (A = high, B = moderate, C = low, or D = very low). Although

dyslipidemia is common in CKD, it not universal to every CKD patient; therefore, establishing a diagnosis and differentiating between hypercholesterolemia with or without hypertriglyceridemia would help to better guide therapy.

4.5.4 Cholesterol-Lowering Treatment

In **adults aged ≥ 50 years with eGFR < 60 mL/min/1.73 m² who are not on dialysis and have not previously received a kidney transplant** (GFR categories G3a-G5), a statin or statin/ezetimibe combination is recommended (grade 1A) (KDIGO Work Group 2013b). This recommendation stems from the findings of the SHARP trial as well as from post-hoc analyses of statin versus placebo trials in the general population where data from the CKD subgroup was extracted for analyses.

The SHARP trial included 9270 participants with CKD (mean eGFR of 27 mL/min/1.73 m²) of who 3023 were on dialysis (Baigent et al. 2011). Patients were randomized to treatment with simvastatin 20 mg plus ezetimibe 10 mg daily or placebo. There was an absolute risk reduction of 2.1% (number needed to treat (NNT) = 48) in the primary outcome of major atherosclerotic events (coronary death, non-fatal myocardial infarction (MI), non-hemorrhagic stroke, or any revascularization procedure) in patients who were treated with the statin/ezetimibe combination compared with placebo after 5 years of follow-up (HR 0.83; 95% CI 0.74–0.94). The primary outcome was driven by significant reductions in ischemic stroke and coronary revascularization. For study participants who were not already on dialysis at the time of randomization, treatment with the statin/ezetimibe combination did not reduce the risk of progression to end-stage renal disease requiring renal replacement therapy.

In **adults aged ≥ 50 years with CKD and eGFR ≥ 60 mL/min/1.73 m²** (GFR categories G1-G2), a statin alone is recommended (grade 1B) (KDIGO Work Group 2013b). This recommendation was made based on the high cardiovascular risk profile of CKD patients who fall within these GFR categories and evidence supporting the efficacy of statins in the general population. Because proteinuria was not always assessed at baseline in these trials, many of them included patients with CKD and eGFR ≥60 mL/min/1.73 m² with proteinuria.

In younger **adults aged 18–49 years with CKD who are not on dialysis and have not previously received a kidney transplant**, it is suggested that statin therapy could be considered in the presence of one or more of the following: known coronary disease (myocardial infarction or coronary revascularization), diabetes mellitus, prior ischemic stroke, or estimated 10-year incidence of coronary death or non-fatal myocardial infarction >10% (grade 2A) (KDIGO Work Group 2013b). Although younger adults are generally at lower risk of cardiovascular complications, the KDIGO Work Group identified four conditions that they felt were of concern and where treatment with a statin may be of benefit.

For **dialysis-dependent patients**, it is suggested that statins or statin/ezetimibe combination not be initiated (grade 2A); however, if a patient is already on a statin

or statin/ezetimibe combination at the time of dialysis initiation, then therapy should be continued (grade 2C) (KDIGO Work Group 2013b). Three large-scale randomized controlled trials of statins in dialysis patients have been published. The first of these is the 4D trial where 1255 HD patients with type 2 diabetes were randomized to receive atorvastatin 20 mg daily or placebo (Wanner et al. 2005). After 4 weeks of treatment and a median follow-up of 4 years, there was no statistically significant reduction in the primary composite endpoint of cardiovascular death, nonfatal MI and stroke despite a reduction in LDL-C levels. The second trial to follow was the AURORA trial which randomized 2776 HD patients to receive rosuvastatin 10 mg daily or placebo (Fellström et al. 2009). Similar to the 4D trial, AURORA also demonstrated no significant effect on the primary composite endpoint of cardiovascular death, nonfatal MI and nonfatal stroke despite a significant reduction in LDL-C. The third paper is the SHARP trial 10, which was described earlier in this section. At the time of randomization, 3023 SHARP trial participants were on dialysis (Baigent et al. 2011). There was no significant reduction in the primary outcome of major atherosclerotic events (coronary death, non-fatal MI, non-hemorrhagic stroke, or any revascularization procedure) in all trial participants as well as in the subgroup of patients who were already on dialysis. However, it was felt that the trial was underpowered for analysis of the dialysis patient subgroup.

None of the above three trials directly address the question of whether statins should be discontinued in patients who are initiating dialysis. Inference is drawn from the 2141 patients who were started on dialysis during the SHARP trial. These patients were included in the non-dialysis group analysis where a significant reduction in the primary endpoint of major atherosclerotic events was noted. Thus, the KDIGO Work Group felt that it would be reasonable to continue statins in patients who are already receiving them at the time of dialysis initiation recognizing that the magnitude of clinical benefit may be lower than in patients with non-dialysis-dependent CKD. In patients where polypharmacy and pill burden may be a concern, discontinuation of the statin or statin/ezetimibe combination may be warranted given the lack of direct evidence that statins are beneficial in dialysis patients,

For **adult kidney transplant recipient**s, statin alone is suggested (grade 2B) (KDIGO Work Group 2013b). This recommendation is based on findings from the ALERT trial as well as other trials that have been done in kidney transplant patients. In the ALERT trial, kidney transplant recipients were randomized to fluvastatin or placebo. The initial dose of fluvastatin used in the trial was 40 mg daily; however, after about 2 years, the fluvastatin dose was doubled to 80 mg daily on recommendation of the independent safety data monitoring board (Fellström et al. 2004). Fluvastatin therapy led to a non-significant reduction in the primary outcome of a major adverse cardiac event (cardiac death, nonfatal MI or coronary intervention procedure) compared to placebo (RR 0.83; 95% CI 0.64–1.06). However, fluvastatin led to a significant absolute risk reduction of 1.7% (NNT = 59) in the secondary endpoint of cardiac death or definite nonfatal MI (HR 0.65; 95% CI 0.48–0.88) and an unblinded extension study found that randomization to fluvastatin was associated with a significant reduction in the original primary outcome after 6.7 years of follow-up.

4.5.5 Triglyceride-Lowering Treatment

The KDIGO guidelines suggest that in **adults with CKD including those on dialysis or who have received a kidney transplant** and hypertriglyceridemia that therapeutic lifestyles changes (TLCs) should be advised (grade 2D) (KDIGO Work Group 2013c). TLCs that are suggested include dietary modification, weight reduction, increased physical activity, reduced alcohol intake, and treatment of hyperglycemia (if present). The evidence for TLCs is weak; however, because they are typically not associated with adverse outcomes and help to improve overall health, the KDIGO Work Group felt that counselling patients with triglyceride levels >5.65 mmol/L about TLCs would be beneficial.

It is no longer recommended that fibric acid derivatives be used for the treatment of severe hypertriglyceridemia to prevent pancreatitis since the evidence supporting the use of these agents is weak and statins appear to prevent pancreatitis in patients with normal or mildly elevated triglycerides. However, in CKD patients who have markedly elevated fasting serum triglyceride levels >11.3 mmol/L, fibric acid derivatives could be considered but the dose of these medications should be adjusted for renal function. Any of the fibric acid derivatives could be used given the lack of evidence to support one over another. Concomitant therapy with both a fibric acid derivative and statin is not recommended in CKD patients due to the increased risk of muscle toxicity.

4.5.6 Statin Dosing and Monitoring

For **CKD patients with an eGFR < 60 mL/min/1.73 m^2 or who are on dialysis**, the KDIGO work group suggests that statin prescription should be based on regimens and doses that have been shown to be beneficial in randomized trials done specifically in this population. The rationale for this suggestion is because of the potential for toxicity with higher statin doses and the relative lack of safety data. For **CKD patients with eGFR ≥ 60 mL/min/1.73 m^2 and who have not previously received a kidney transplant**, the KDIGO Work Groups suggests that these patients may be treated with any statin regimen that is approved for use in the general population (see Table 4.4) (KDIGO Work Group 2013b).

The KDIGO Work Group advises against the adjustment of statin doses based on LDL-C levels given the lack of evidence to support a specific LDL-C target while on statin therapy. They recommend that baseline transaminase levels should be measured regardless of CKD severity although routine follow-up levels are not required. The measurement of CK levels at baseline or during follow-up is not required as per the KDIGO Work Group unless the patient develops symptoms suggestive of myopathy.

Table 4.4 Recommended doses (mg/day) of statins in adults with CKD

Statin	eGFR G1-G2	eGFR G3a-G5, including dialysis patients or kidney transplant recipients
Atorvastatin	General population	20[1]
Fluvastatin	General population	80[2]
Lovastatin	General population	Not studied
Pitavastatin	General population	2
Pravastatin	General population	40
Rosuvastatin	General population	10[3]
Simvastatin	General population	40
Simvastatin/ Ezetimibe	General population	20/10[4]

Adapted from the KDIGO Clinical Practice Guideline for Lipid Management in CKD 2013 (Wanner and Tonelli 2014)
Dose based on [1]4D, [2]ALERT, [3]AURORA, [4]SHARP. Note that not all statins are available in all countries

4.6 Fluid, Electrolyte, and Acid-Base Disorders in CKD

4.6.1 Introduction

One of the key functions of the kidney is to maintain fluid, electrolyte and acid-base balance within the body. The kidneys are responsible for the excretion of water and excess minerals that may be consumed through the diet. They also play a crucial role in calcium homeostasis. The focus of this section will be on sodium and water, potassium, magnesium and acid-base balance disorders. Phosphate and calcium homeostasis are covered in the chronic kidney disease-mineral and bone disorder (CKD-MBD) section.

4.6.2 Sodium and Water

In people with normal kidney function, the tubular excretion of filtered sodium and water matches their intake resulting in the maintenance of sodium levels within the usual range. However, in patients with impaired kidney function, this sodium-water balance is disrupted. Typically, sodium excretion is unaffected until the GFR reaches less than 15 mL/min due to the presence of adaptive mechanisms within the body. The fractional excretion of sodium in the urine is increased by the remaining func-

tioning nephrons in proportion to the loss of glomerular filtration. However, as kidney disease progresses, sodium retention and resultant extracellular fluid volume (ECFV) expansion may arise from decreased urinary sodium excretion. This ECFV expansion may cause edema and hypertension, which may further accelerate damage to the nephron. If exogenous water intake does not exceed the handling mechanisms of the kidney, then the ECFV expansion will be isotonic and the serum sodium level will remain within the normal range. However, in the setting of excess water intake, hyponatremia may be seen. Thus, patients may need to be counselled on appropriate sodium and water restriction (Bargman and Skorecki 2018).

Both hyponatremia (serum Na < 135 mmol/L) and hypernatremia (serum Na > 145 mmol/L) may develop in CKD patients although hyponatremia occurs more commonly. Hypernatremia usually results from either a loss of free water due to excessive urinary or other body water losses, or inadequate free water intake from impaired thirst mechanism or limited access to water. Rarely does hypernatremia occur as a result of excess sodium intake. On the other hand, hyponatremia is caused by a decrease in the reabsorption of sodium by the kidneys and this may or may not be accompanied by a change in volume status. Most frequently, hyponatremia in CKD patients is dilutional from excessive free water intake or intake of other hypotonic fluids. For these patients, treatment with a loop diuretic, e.g. furosemide, bumetanide, or ethacrynic acid, may be necessary and the doses used in this patient population are often higher than those used in people with normal renal function. Combination therapy with a loop diuretic and metolazone may be useful in patients with refractory hyponatremia. Thiazide diuretics alone are ineffective when the GFR falls below 30 mL/min. In patients on maximal doses of diuretics with intractable edema and hypertension, dialysis initiation may need to be considered (Bargman and Skorecki 2018; Khan et al. 2016; Mahaldar 2012; Dhondup and Qian 2017; Garrard and Jones 2018).

4.6.3 Potassium

Hyperkalemia (serum K > 5 mmol/L) is one of the most common and life-threatening electrolyte complications of CKD. It occurs more frequently than hypokalemia (serum K < 3.5 mmol/L). Due to compensatory mechanisms within the body, serum potassium levels usually remain within the normal range until patients reach end-stage renal disease (ESRD). The workload of each remaining functioning nephron and the potassium excretion via the gastrointestinal tract (feces) are both increased. Hyperkalemia most commonly results from an increase in dietary potassium intake with a concomitant decrease in urinary potassium excretion; however, there are a number of other conditions that may worsen hyperkalemia. A non-comprehensive list of these conditions include: insulin deficiency, tissue breakdown, e.g. hemolysis and tumor lysis syndrome, metabolic acidosis, and medications that alter renal potassium excretion, e.g. angiotensin-converting enzyme inhibitors or ACEIs, angiotensin II receptor blockers or ARBs, potassium-sparing diuretics, aldosterone

receptor antagonists and calcineurin inhibitors. ACEIs and ARBs are often prescribed in CKD patients; however given the risk of hyperkalemia, benefits versus risks of utilizing these medications should be weighed. Close monitoring of serum potassium levels may be required (Bargman and Skorecki 2018; Mahaldar 2012; Reddi 2018a).

Because of the chronicity with which hyperkalemia is seen in CKD patients, it is usually better tolerated from a symptom perspective than in patients who present acutely with hyperkalemia. Often CKD patients may be asymptomatic until much higher serum potassium levels are reached. Clinical manifestations of hyperkalemia may be classified into those that are neuromuscular, i.e. muscle weakness and paralysis, cardiac or metabolic in nature. Electrocardiogram (ECG) changes may not be noticeable until serum potassium levels exceed 6.5 mmol/L. At this level, peaked T waves, prolonged PR interval and widening of QRS complex may be seen. Treatment measures should be implemented according to patient symptoms and the presence of ECG changes. In patients who are asymptomatic and have no ECG changes, dietary potassium restriction, discontinuation of medications that may be contributing to the hyperkalemia, and treatment with a hyperkalemia exchange resin such as sodium polystyrene sulfonate or calcium polystyrene sulfonate could be trialed. However, where symptoms of hyperkalemia or where ECG changes are evident, more immediate treatment measures should be implemented. These include the use of intravenous calcium gluconate to stabilize the myocardium, and intravenous insulin and dextrose, inhaled salbutamol, and intravenous sodium bicarbonate (if acidosis is present), to shift potassium intracellularly. Hemodialysis (HD) may be required in ESRD patients who are non-responsive to these treatments (Mahaldar 2012; Garrard and Jones 2018; Reddi 2018a).

4.6.4 Magnesium

Both hypermagnesemia (serum Mg > 1.1 mmol/L) and hypomagnesemia (serum Mg < 0.7 mmol/L) may be seen in CKD patients. Hypermagnesemia occurs more commonly in patients with advanced CKD and in ESRD patients on HD whereas hypomagnesemia occurs more commonly in ESRD patients on peritoneal dialysis (PD). As kidney function starts to decline, serum magnesium levels will increase due to the decreased ability of the kidney to excrete magnesium; thus, the intake of magnesium-containing foods and medications may need to be limited. Patients should be counselled to avoid taking vitamins that contain magnesium, extra magnesium supplements and magnesium-containing antacids or laxatives. Signs and symptoms of hypermagnesemia may not be obvious until serum magnesium levels reach 1.5 mmol/L where patients may present with nausea and vomiting. More serious complications of absent reflexes, respiratory paralysis, coma, and cardiac arrest may be seen at even higher serum magnesium levels. In the absence of signs or symptoms of hypermagnesemia, removal of the cause will usually normalize serum magnesium levels; however, in a symptomatic patient, calcium gluconate adminis-

tration and possibly treatment with hemodialysis may be required. In PD patients, there is a tendency towards hypomagnesemia due to the daily use of low magnesium concentration PD solutions. As well, in PD patients who maintain residual kidney function, loop diuretics may be prescribed and this may further exacerbate the hypomagnesemia (Dhondup and Qian 2017; Garrard and Jones 2018; Oliveira et al. 2018; Reddi 2018b; Amirmokri et al. 2007).

4.6.5 Acid-Base Balance

Metabolic acidosis (serum bicarbonate <22 mmol/L) occurs more commonly in CKD patients than metabolic alkalosis and affects almost all organ systems. Cardiovascular, neurologic, respiratory and other complications may arise from the development of metabolic acidosis. In an average-sized adult with normal functioning kidneys, the renal tubules reabsorb ~4500 mmol of filtered bicarbonate daily and generate ~80 mmol of bicarbonate to neutralize daily acid production. The kidneys also remove excess acid from the body through ammonia genesis and excretion. However, as kidney function declines, bicarbonate reabsorption and generation is decreased while endogenous acid production remains unchanged. A reduction in the number of functioning nephrons in CKD further compromises excess acid excretion by way of ammonia genesis. Initially, each remaining functioning nephron tries to compensate by generating a larger amount of ammonia but eventually, this mechanism will fail at which point the prescription of oral sodium bicarbonate may be required. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend an oral sodium bicarbonate dose of 0.5–1 mEq/kg/day to achieve a sodium bicarbonate level of 22 mmol/L. Patients on sodium bicarbonate therapy will need to be closely monitored for volume overload and worsened blood pressure control. If the metabolic acidosis is due to renal failure, then treatment with dialysis will correct the condition and sodium bicarbonate therapy can usually be stopped at the time of dialysis initiation (Mahaldar 2012; Dhondup and Qian 2017; Garrard and Jones 2018; Łoniewski and Wesson 2014; Reddi 2018c).

4.7 CKD and Nutrition

4.7.1 Introduction

The kidneys are involved in many important functions within the body including the excretion of metabolic waste products, and the regulation of fluid, electrolyte and acid-base balance. When kidney function is impaired, patients may develop complications from the build-up of these waste products, also referred to as uremic toxins,

as well as disturbances of fluid, electrolyte and acid-base balance. The accumulation of uremic toxins may cause nausea and vomiting, decreased appetite, and an altered sense of taste. As a result, patients may become anorexic and quite severely malnourished as their kidney disease progresses. The term "protein-energy wasting" has been used in the renal nutrition literature to describe the loss of body protein mass and fuel reserves in patients with end-stage renal disease (ESRD). Protein-energy wasting or malnutrition has been shown to increase morbidity and mortality in this patient population (Obi et al. 2015). Thus, renal dietitians play a crucial role in the care of chronic kidney disease (CKD) patients. Early nutritional intervention is vital to delaying the progression of CKD. Additional dietary counselling may be required as kidney function declines to correct any electrolyte and acid-base abnormalities while trying to maintain adequate protein and caloric intake. The dietary needs of CKD patients will need to be individualized and vary depending on the stage of their kidney disease as well as dialysis modality. In this section, we will review the nutritional recommendations for CKD predialysis and dialysis patients as per the guidelines published by the various dietetic and renal societies.

4.7.2 Protein Intake

When protein is ingested, nitrogenous waste products are produced as a result of its breakdown. Healthy kidneys have millions of nephrons that help to filter out these waste products and remove them from the body via the urine; however, this function is impaired in patients who have kidney disease. In CKD predialysis patients, restricting protein intake will help to reduce the production of these toxic byproducts. As well, protein restriction decreases acid formation and resultant metabolic acidosis, and possibly delays the progression of kidney failure and need for renal replacement therapy through decreased workload to the kidney. Consumption of large amounts of protein has been shown to increase intraglomerular pressure and glomerular hyperfiltration with consequent damage to the glomeruli (Kalantar-Zadeh and Fouque 2017; Bellizzi et al. 2018). The general recommendation for daily dietary protein intake in CKD predialysis patients is 0.6–0.8 g/kg/day if the patient does not have diabetes. If the patient is diabetic, then a higher daily protein intake of 0.8–1 g/kg/day may be required. The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines further specify that at least 50% of the protein content should be of high biological value. Protein foods that are considered to be of high biological value are those from animal sources, e.g. red meats, chicken, fish and eggs, that contain the essential amino acids (Chronic Kidney Disease Evidence-Based Nutrition Practice Guidelines 2010; European Guidelines for the Nutritional Care of Adult Renal Patients 2002; KDOQI Clinical Practice Guideline for Nutrition in Chronic Renal Failure 2000; Chronic Kidney Disease (CKD) and Diet: Assessment, Management, and Treatment 2015).

Once a patient is started on dialysis, protein needs will be higher due to the removal of amino acids, peptides and protein during the dialysis process. Thus, the recommended daily dietary protein intake of dialysis patients is higher than that of CKD predialysis patients at 1.1–1.2 g/kg/day. There is also a subtle difference between hemodialysis (HD) and peritoneal dialysis (PD) patients with a higher protein intake recommended in PD patients of 1.2–1.3 g/kg/day due to higher protein losses with this dialysis modality. Where possible, it is recommended that PD patients try to consume at least 1.3 g protein/kg/day unless adequate protein nutritional status is achieved on a 1.2 g protein/kg/day diet. In PD, about 5–15 g of protein is lost each day and this may be even higher during a peritonitis episode whereas the protein loss in HD is much lower at ≤1–3 g per dialysis session. The same recommendation for CKD predialysis patients pertaining to the intake of protein foods that are at least 50% high biological value also applies to dialysis patients. In some cases where dialysis patients are unable to meet their protein and energy requirements for an extended period of time, then nutrition support in the form of oral nutritional supplements, e.g. Nepro® or protein powder, tube feeds, intradialytic parenteral nutrition, or total or partial parenteral nutrition may be required (European Guidelines for the Nutritional Care of Adult Renal Patients 2002; KDOQI Clinical Practice Guideline for Nutrition in Chronic Renal Failure 2000; Fouque et al. 2007; Dombros et al. 2005).

4.7.3 Caloric Intake

The energy expenditure of CKD patients is similar to that of normal, healthy individuals; thus, the recommended dietary allowance is approximately the same for people who are of an equivalent age regardless of kidney function. A daily energy intake of about 35 kcal/kg/day is recommended for all three groups of CKD patients, i.e. predialysis, HD and PD. For people over the age of 60 years, a lower daily energy intake of 30–35 kcal/kg/day may be sufficient as per the KDOQI guidelines because elderly people tend to be more sedentary. The recommended daily energy intake of 35 kcal/kg/day was derived from metabolic balance studies of CKD patients where energy consumption that was maintained at this level was sufficient to ensure a neutral nitrogen balance as well as adequate serum albumin and anthropometric indices. As discussed earlier in the protein intake section, in patients who are unable to attain the recommended energy intakes, then oral nutritional supplements that are high in energy, tube feeds, or parenteral nutrition may be required after dietary counselling has been trialed (Chronic Kidney Disease Evidence-Based Nutrition Practice Guidelines 2010; European Guidelines for the Nutritional Care of Adult Renal Patients 2002; KDOQI Clinical Practice Guideline for Nutrition in Chronic Renal Failure 2000; Fouque et al. 2007; Dombros et al. 2005).

4.7.4 Sodium and Fluid Intake

Sodium and fluid restriction may be necessary if blood pressure or fluid retention is a concern. The recommended daily sodium intake for CKD patients with hypertension is the same as that for people with normal kidney function and hypertension, and ranges between 2000 and 2300 mg/day depending on the guideline that is referred to. Reduced dietary sodium intake decreases the feeling of thirst and subsequent urge to drink fluids. As a result, blood pressure control improves and damage to the nephrons is reduced. The majority of dietary sodium comes from salt or mono sodium glutamate (MSG) that has been added to food. Most convenience and processed foods contain added salt; therefore, consumption of these products should be limited whenever possible. In terms of fluid intake, for CKD predialysis patients, there is no restriction unless the patient is edematous or if it is medically indicated for another concurrent condition such as heart failure. For dialysis patients, guidelines for daily fluid intake vary between 500–1000 mL in addition to a patient's daily urine output volume. Typically, fluid restrictions are more lax in PD and home HD patients where dialysis hours are increased. Fluid restrictions should be individualized and take into consideration a patient's living environment as well as their clinical status. For example, patients living in hotter climates or during periods of hot weather may need to consume more water to replace their insensible losses. When determining daily fluid consumption, patients should be instructed to include all foods that are liquid at room temperature. An important point to keep in mind is that the key to controlling fluid intake is to minimize dietary sodium consumption (European Guidelines for the Nutritional Care of Adult Renal Patients 2002; Chronic Kidney Disease (CKD) and Diet: Assessment, Management, and Treatment 2015; Fouque et al. 2007; Dombros et al. 2005).

4.7.5 Potassium Intake

As kidney disease progresses, patients are at increased risk of developing hyperkalemia due to decreased urinary potassium excretion. Thus, in patients with advanced CKD not on dialysis and in those on conventional HD (12 h/week of dialysis), dietary potassium intake may need to be restricted (see Table 4.5 for a list of high potassium foods). If this is unsuccessful, then the prescription of hyperkalemia exchange resins may be required. Salt substitutes, which consist of potassium chloride, should not be used by CKD patients. The recommended daily dietary potassium intake as per the Dietitians' Special Interest Group of the European Dialysis and Transplantation Nurses Association/European Renal Care Association (EDTNA) is 2000–2500 mg/day (50–65 mmol/day). Alternatively, the European Best Practice Guidelines (EBPG) for HD patients recommends a daily potassium intake of 1950–2730 mg/day (50–70 mmol/day) or 1 mmol/kg IBW/day. Potassium restriction is generally not required in PD and home HD patients due to efficient potassium removal via daily dialysis in PD patients or increased dialysis hours for

Table 4.5 High potassium foods

Fruits	Vegetables	Others
Bananas	Potatoes	Dried beans and legumes (Split peas, baked beans, lentils, kidney beans, chick peas, etc.)
Oranges or orange juice	Sweet potatoes/yams	Nuts, peanut butter or seeds
Cantaloupe or honeydew	Dark leafy greens: spinach, Swiss chard, beet greens	Dairy products: milk, yogurt, milk pudding and ice cream, cottage cheese
Kiwi fruit	Tomato sauce/paste	Molasses
Pomegranate	Tomato juice/V-8®	Bran
Avocado	Tomato, fresh (more than ½ medium)	Potato chips
Dried fruit: dates, prunes, raisins		French fries
		Chocolate
		Coffee (more than 2 cups/day)

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home HD patients. These patients in fact may need high potassium diets and possibly potassium supplementation. It should be kept in mind that dietary potassium restrictions should be individualized based on a patient's bloodwork. The BC Provincial Renal Agency (BCPRA) has produced helpful resources on potassium and the kidney diet that can be distributed to CKD predialysis, HD and PD patients. These references are available at http://www.bcrenalagency.ca/health-info/managing-my-care/diet (European Guidelines for the Nutritional Care of Adult Renal Patients 2002; Fouque et al. 2007; Healthy Eating For Your Kidneys 2018; Diet For Hemodialysis 2018; Diet For Peritoneal Dialysis 2018; Potassium and Your Kidney Diet – Advanced 2016; Potassium and Your Kidney Diet – Basic 2016).

4.7.6 Phosphorus Intake

Similar to potassium, phosphorus is also excreted by the kidneys; thus, with progression of kidney disease, hyperphosphatemia may ensue. High phosphate levels may be managed through dietary phosphorus restriction, prescription of phosphate binders or treatment with dialysis. In home HD patients who usually dialyze ≥20 h/week, such effective phosphate removal is achieved that the addition of phosphate to the dialysate bath may be necessary in addition to consuming a high phosphorus diet. Depending on the guidelines that are referred to, there are slight variances in the recommended daily dietary phosphorus intake. The Academy of Nutrition and Dietetics guidelines as well as the EBPG for HD patients recommend a daily dietary phosphorus intake of 800–1000 mg/day. On the other hand, the EDTNA guidelines suggest a phosphorus intake of 600–1000 mg/day for CKD pre-dialysis patients and

Table 4.6 High phosphorus foods

High phosphorus foods	Serving size
Cow's milk	½ cup
Soy milk	¾ cup
Chocolate milk / hot chocolate	½ cup
Yogurt (plain or fruit)	½ cup
Cheese (cheddar, mozzarella)	1 ounce (1 inch cube)
Cottage cheese	1/3 cup
Ice cream	¾ cup
Pudding or custard	½ cup
Pizza (cheese or vegetarian)	½ of 1 medium slice
Dried beans (kidney, white, garbanzo)	½ cup
Nuts	3 tbsp
Peanut butter and other nut butters	2 tbsp
Sunflower seeds	2 tbsp
Pumpkin seeds	1 tbsp
Bran Flakes	2/3 cup
All Bran® cereal	¼ cup
Bran muffin	1 medium
Commercial waffles and pancakes	1
Sardines	2
Liver and organ meats	1 ounce
These high phosphorus foods contain between 100 and 140 mg of phosphorus per serving.	

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1000–1400 mg/day for HD and PD patients. Maintaining a phosphorus restricted diet is challenging as phosphorus is present in almost all living organisms; therefore, it is found in most foods. There are two main forms of phosphorus: (1) organic and (2) inorganic. Phosphorus is naturally found in foods that are rich in protein, i.e. animal-based foods as well as plant foods. Animal foods that are abundant in organic phosphorus include meat, poultry, fish and dairy products, and examples of plant foods include seeds, nuts, and legumes (see Table 4.6 for a list of high phosphorus foods). Inorganic phosphorus is found in many preservatives and additive salts in processed foods; thus, patients should be encouraged to consume fresh foods whenever possible (Chronic Kidney Disease Evidence-Based Nutrition Practice Guidelines 2010; European Guidelines for the Nutritional Care of Adult Renal Patients 2002; Fouque et al. 2007; Kalantar-Zadeh et al. 2010).

4.7.7 Vitamin Supplementation

Inadequate nutritional intake as well as removal of the water-soluble vitamins during dialysis treatment may put patients at risk of micronutrient deficiency. Thus, all dialysis patients are prescribed a specially formulated vitamin supplement for CKD

patients known as Replavite®. These vitamins consist of B vitamins (B1 – thiamine, B2 – riboflavin, B3 – niacinamide, B5 – pantothenic acid, B6 – pyridoxine, B12 – cyanocobalamin, biotin), vitamin C 100 mg and folic acid 1 mg. Conventional HD and PD patients are usually prescribed Replavite® 1 tablet/day whereas home HD patients who dialyze ≥20 h/week are prescribed Replavite® 2 tablets/day. CKD predialysis patients are not routinely prescribed these vitamins unless they are unable to maintain adequate dietary intake of required vitamins. Over-the-counter multivitamin preparations should not be taken prior to consultation with a pharmacist or renal dietitian (Comparison of Multivitamin Preparations 2018).

4.8 Symptoms and CKD

4.8.1 Introduction

The kidneys are involved in a multitude of functions within the body including the regulation of electrolyte, fluid and acid-base balance, the excretion of wastes and toxins, the production of hormones and the control of blood pressure. As the kidneys start to fail, patients may develop symptoms of chronic kidney disease (CKD) or symptoms related to the build-up of uremic toxins. Signs and symptoms of CKD are usually nonspecific and often do not present until late in the course of CKD (see Table 4.7).

Table 4.7 Uremic Symptoms by Body Systems

Body system	Symptoms
Constitutional	Fatigue, malaise, weakness
Eyes, ears, nose, mouth throat	Taste disturbances, uremic odor
Cardiovascular	Angina, arrhythmias, atherosclerosis, congestive heart failure, hypertension, pericarditis, peripheral and pulmonary edema
Respiratory	Shortness of breath, pleuritis
Gastrointestinal	Anorexia, nausea/vomiting, delayed gastric emptying, gastrointestinal bleeding, weight loss
Genitourinary	Amenorrhea and sexual dysfunction (decreased libido, impotence), changes in urination, frothy urine (proteinuria), hematuria
Musculoskeletal	Leg cramps, restless legs syndrome
Skin	Calciphylaxis, dry skin, pruritus, skin pallor
Neurological	Encephalopathy (asterixis, ataxia, decreased mental acuity, delirium, slurred speech, tremors), headaches, peripheral neuropathy, seizures, sleep disturbances, coma
Psychiatric	Anxiety, depression, psychosis
Endocrine	Mineral and bone disorder (hypocalcemia, hyperphosphatemia, hyperparathyroidism, vitamin D deficiency), insulin resistance
Hematologic	Anemia, immune suppression, platelet dysfunction
Other	Electrolyte abnormalities: hyperkalemia, hypermagnesemia, metabolic acidosis

Symptom burden is a major concern in CKD patients as it often impacts a patient's life negatively. In 2013, the Kidney Disease: Improving Global Outcomes (KDIGO) organization held a Controversies Conference on Supportive Care in CKD to discuss issues related to the international application of supportive medicine to CKD patients with the ultimate goal of working toward the development of globally applicable guidelines. One of the key areas of discussion was symptom assessment and management. A review of the literature was undertaken to identify symptoms in CKD and their prevalence rate. The most prevalent symptom was sleep disorders at 60% followed by pain at 58%, anorexia at 56%, nausea at 46%, uremic pruritus at 41%, constipation at 40%, vomiting at 23%, depression at 22% in CKD patients and 23% in dialysis patients, diarrhea at 21%, and restless legs syndrome at 10–20%. The KDIGO Work Group recommend that regular global symptom screening should be incorporated into routine clinical practice and that symptom management should follow a stepwise approach with first-line treatment being non-pharmacological interventions and second-line treatment being pharmacologic therapy (Davison et al. 2015).

In British Columbia (BC), Canada, extensive work has been done in the area of symptom assessment and management including the development of a guideline specifically to address this issue as well as individual treatment algorithms and patient teaching tools for some of the more commonly encountered CKD symptoms. We will start off by reviewing the Edmonton Symptom Assessment System (ESAS)-revised: Renal, which was the symptom screening tool selected for use provincially in BC, then briefly discuss the management of each of the following symptoms: fatigue/insomnia, pain, nausea, uremic pruritus, constipation, muscle cramps, and restless legs syndrome.

4.8.2 Symptom Assessment

The recommendations of the BC Provincial Renal Agency (BCPRA) Systematic Symptom Assessment and Management guidelines are as follows (Systematic Symptom Assessment and Management (using the Modified Edmonton Symptom Assessment System) 2017):

1. Utilize the modified Edmonton Symptom Assessment Score (mESAS) to assess the symptom burden of patients who meet the following criteria: eGFR <15 mL/min/1.73^2 and/or reporting significant CKD-related symptoms.
2. Administer the mESAS to patients who meet the criteria in recommendation #1 every 6 months or more frequently as indicated by the patient's condition.
3. Review the mESAS and for symptom scores of ≥4, complete a detailed assessment of the symptom(s) and develop a symptom(s) management plan (symptom score of 1–3 = mild, symptom score of 4–6 = moderate and symptom score of 7–10 = severe).
4. Provide information to the patient's primary care provider about their symptoms and severity.

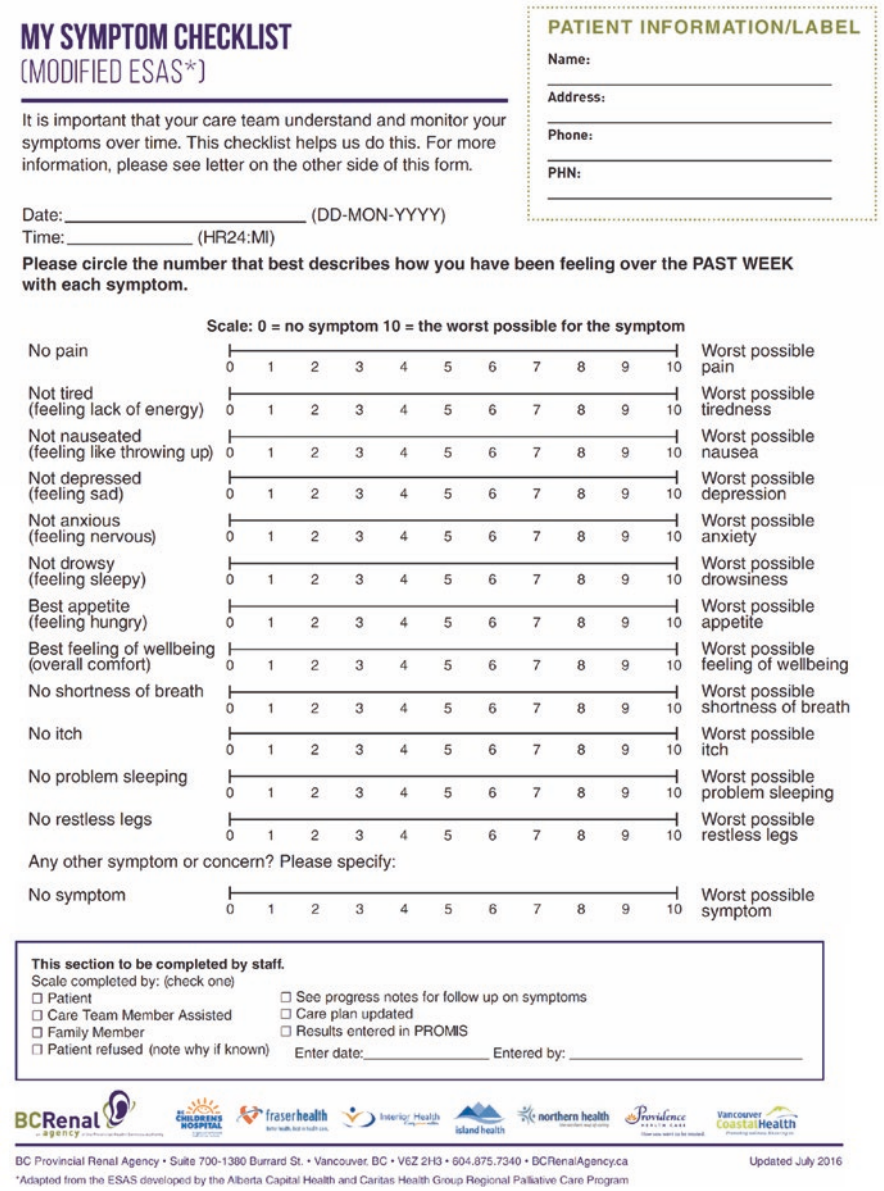
The ESAS is a clinically validated symptom measurement tool that has been used extensively in other chronic disease states. The original tool was developed by the Regional Palliative Care Program, Capital Health in Edmonton, Alberta, Canada. The current version used within the kidney programs in BC has been modified slightly to include symptoms that are more relevant to renal patients. The mESAS consists of 12 symptom-related questions and 1 open-ended question (see Fig. 4.1). Patients are asked to rate their symptoms over the past week between 0 (no symptoms) and 10 (severe symptoms). In BC, the patient-friendly title of the tool is "My Symptom Checklist" and the tool is available in multiple languages on the BCPRA website (http://www.bcrenalagency.ca/health-professionals/clinical-resources/symptom-assessment-and-management). Because symptom burden is often underreported in CKD patients, utilizing the mESAS helps patients and the healthcare team to identify symptoms that patients may be experiencing so that appropriate treatment strategies can be implemented. Also, assessment for symptom improvement can be made more systematically with the use of such a screening tool as the changes in patient symptom scores can be compared between their initial mESAS survey and subsequent ones.

4.8.3 Symptom Management

Treatment algorithms and patient teaching tools have been developed by the BCPRA for each of the following symptoms of fatigue/insomnia, pain, nausea, uremic pruritus, constipation, muscle cramps and restless legs syndrome. These treatment algorithms and patient teaching tools can be accessed on the BCPRA website: http://www.bcrenalagency.ca/health-professionals/clinical-resources/symptom-assessment-and-management. Highlights of these treatment algorithms and patient teaching tools are summarized below.

4.8.4 Fatigue/Insomnia

Fatigue is commonly reported in CKD patients. It may result from many different causes but encouraging patients to get a good night's sleep is important. When assessing a patient with fatigue, it is essential to ask about sleep symptoms (latency, total sleep time, early and/or frequent waking, daytime impact) and duration, perform a sleep hygiene assessment, review medical history for exacerbating conditions, e.g. obstructive sleep apnea, restless legs, pruritus, pain, and/or mood disorder, and obtain medication history for medications that may cause insomnia. Non-pharmacological strategies should be trialed for at least 2–4 weeks prior to the prescription of pharmacologic agents. Measures to promote good sleep hygiene should be encouraged, e.g. avoiding caffeine after lunch, avoiding alcohol and smoking, trying not to eat large meals around bedtime, etc. (refer to the BCPRA Management



MY SYMPTOM CHECKLIST
(MODIFIED ESAS*)

It is important that your care team understand and monitor your symptoms over time. This checklist helps us do this. For more information, please see letter on the other side of this form.

PATIENT INFORMATION/LABEL

Name: _____

Address: _____

Phone: _____

PHN: _____

Date: _____ (DD-MON-YYYY)

Time: _____ (HR24:MI)

Please circle the number that best describes how you have been feeling over the PAST WEEK with each symptom.

Scale: 0 = no symptom 10 = the worst possible for the symptom

No pain	0 1 2 3 4 5 6 7 8 9 10	Worst possible pain
Not tired (feeling lack of energy)	0 1 2 3 4 5 6 7 8 9 10	Worst possible tiredness
Not nauseated (feeling like throwing up)	0 1 2 3 4 5 6 7 8 9 10	Worst possible nausea
Not depressed (feeling sad)	0 1 2 3 4 5 6 7 8 9 10	Worst possible depression
Not anxious (feeling nervous)	0 1 2 3 4 5 6 7 8 9 10	Worst possible anxiety
Not drowsy (feeling sleepy)	0 1 2 3 4 5 6 7 8 9 10	Worst possible drowsiness
Best appetite (feeling hungry)	0 1 2 3 4 5 6 7 8 9 10	Worst possible appetite
Best feeling of wellbeing (overall comfort)	0 1 2 3 4 5 6 7 8 9 10	Worst possible feeling of wellbeing
No shortness of breath	0 1 2 3 4 5 6 7 8 9 10	Worst possible shortness of breath
No itch	0 1 2 3 4 5 6 7 8 9 10	Worst possible itch
No problem sleeping	0 1 2 3 4 5 6 7 8 9 10	Worst possible problem sleeping
No restless legs	0 1 2 3 4 5 6 7 8 9 10	Worst possible restless legs

Any other symptom or concern? Please specify:

No symptom	0 1 2 3 4 5 6 7 8 9 10	Worst possible symptom

This section to be completed by staff.

Scale completed by: (check one)

- ☐ Patient
- ☐ Care Team Member Assisted
- ☐ Family Member
- ☐ Patient refused (note why if known)

- ☐ See progress notes for follow up on symptoms
- ☐ Care plan updated
- ☐ Results entered in PROMIS

Enter date: _____ Entered by: _____

BCRenal agency

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Updated July 2016

*Adapted from the ESAS developed by the Alberta Capital Health and Caritas Health Group Regional Palliative Care Program

Fig. 4.1 BC Provincial Renal Agency "My Symptom Checklist" (Modified ESAS) (My Symptom Checklist 2016)

of Fatigue/Insomnia in Patients with CKD (Management of Fatigue/Insomnia In Patients With Chronic Kidney Disease 2017). Patients should also be encouraged to engage in physical activity. If non-pharmacological strategies fail after an adequate trial, then pharmacologic agents could be considered. Melatonin, a natural health product, has been used successfully in some patients. The usual starting dose is 3 mg orally hs prn and if ineffective, the dose could be uptitrated. If fatigue/insomnia persists, then prescription of a sleep aid in the short-term may be beneficial. The following sedatives have been used in CKD patients with no dosage adjustment required: zopiclone 3.75–5 mg orally hs prn or trazodone 25–100 mg orally hs prn. Short-acting benzodiazepines are generally reserved as last-line therapy (Management of Fatigue/Insomnia In Patients With Chronic Kidney Disease 2017; Patient Teaching Tool – Fatigue 2017).

4.8.5 Pain

The prevalence of chronic pain in CKD patients is quite high and it may or may not be directly related to the patient's kidney disease. Often, the pain results from other underlying medical conditions. Thus, it is important to take an accurate history to decide on the most optimal treatment strategy. If there is an identifiable cause, then this should be addressed if possible. The PQRST pneumonic is helpful when trying to remember all the questions to ask patients about their pain. The "P" stands for precipitating/alleviating factors, the "Q" stands for quality of pain, the "R" stands for radiation of pain, the "S" stands for site and severity of pain, and the "T" stands for timing/onset of pain and whether it is constant/intermittent pain (Raina et al. 2018). Depending on the type of pain that a patient is experiencing, then treatment that specifically targets these symptoms should be prescribed.

The BCPRA has published an algorithm titled "BCPRA Guidelines and Drug Choices for Chronic Pain in Dialysis Patients" (BCPRA Guidelines and Drug Choices for Chronic Pain in Dialysis Patients 2017) whereby a stepwise approach, similar to the World Health Organization stepladder approach to analgesia, is outlined for musculoskeletal/nociceptive pain and a second algorithm for neuropathic pain. For the management of musculoskeletal/nociceptive pain, non-opioid analgesics and/or an adjuvant are recommended as first line treatment in patients with a pain score of 1–4 out of 10 and if the pain is not controlled or the initial pain score is ≥5 out of 10, then an opioid could be added to the non-opioid analgesic and/or adjuvant. The preferred non-opioid analgesic in CKD patients is acetaminophen. Topical analgesics such as topical NSAIDs (diclofenac gel) or capsaicin cream could also be considered. For long-term opioid use, buprenorphine, fentanyl and methadone are preferred as they do not have any active metabolites. However, patients would need to reach an adequate narcotic dose before they could be converted to one of these agents. For opioid initiation and uptitration, the use of hydromorphone or oxycodone is preferable in CKD patients. Although these opioids are safer than morphine or codeine in terms of risk of accumulation of neurotoxic metabolites, central nervous system side effects may still be seen at higher doses

(Raina et al. 2018; BCPRA Guidelines and Drug Choices for Chronic Pain in Dialysis Patients 2017; Preferred Medications in Chronic Kidney Disease 2018; Renal Analgesic Brochure 2011).

Neuropathic pain is defined by the presence of four or more of the following symptoms: burning pain, pain to cold, electric shocks, tingling, pins and needles, numbness, itching, increased pain with light touch, or decreased sensation. For patients with a pain score of 1–4 out of 10, treatment with gabapentin is recommended first-line. If the pain is localized, capsaicin cream 0.025% or 0.075% could be considered. If pain control is inadequate at the target dose for 2–4 weeks or the initial pain score is ≥5 out of 10, then nortriptyline/desipramine, nabilone, topiramate or pregabalin could be trialed. Dosing information for all of these drugs is available on the BCPRA Guidelines and Drug Choices for Chronic Pain in Dialysis Patients algorithm (BCPRA Guidelines and Drug Choices for Chronic Pain in Dialysis Patients 2017) as well as in the BCPRA Renal Analgesic Brochure (Renal Analgesic Brochure 2011).

4.8.6 Nausea

Nausea and vomiting are very common in CKD patients and is multifactorial. The inability of CKD patients to clear uremic toxins from the body may be a contributing factor. Appropriate history should be taken from the patient to ascertain the duration and frequency of nausea, and if it is accompanied by vomiting, abdominal pain, or constipation. If any contributing factors are identified, these should be addressed first. A thorough review of the patient's medications should be done to determine if any are causing the nausea/vomiting, and an attempt at therapy substitution should be made if this is the case. For patients who are on dialysis, dialysis adequacy should be assessed as underdialysis results in the accumulation of uremic toxins and subsequent nausea/vomiting. Non-pharmacological strategies such as reducing or eliminating potentially nauseating stimuli, eating frequent small high calorie meals or snacks, and sitting upright or reclined with the head elevated for 30–60 min after meals should be trialed first (see the BCPRA Management of Nausea in Patients with CKD algorithm for a full list of recommendations) (Management of Nausea In Patients With Chronic Kidney Disease 2017). If these measures are inadequate, then the prescription of an antiemetic such as haloperidol or methotrimeprazine may be appropriate. Ondansetron could also be considered if both of these options are ineffective; however, it is expensive and there is a risk of QT prolongation. Dimenhydrinate is considered to be ineffective for the treatment of CKD-related nausea/vomiting as this condition is felt to be caused by chemoreceptor activation and dimenhydrinate is more effective for nausea/vomiting caused by vestibular dysfunction, motor disorder and increased intracranial pressure. If the nausea and/or vomiting are gastroparesis-related, a trial of metoclopramide or domperidone may be warranted (Management of Nausea In Patients With Chronic Kidney Disease 2017).

4.8.7 Uremic Pruritus

Pruritus or skin itching is common in patients with and without kidney disease. Some patients may have easily visible areas of the skin that are affected whereas others may complain of skin itching with no obvious signs. History taking is crucial to characterize the pruritus. If specific contributing factors of pruritus are identified, e.g. elevated phosphorus levels or inadequate dialysis, then correcting the underlying problem may be more effective in resolving the pruritus. If primary lesions are present, it is recommended that the patient be referred to a dermatologist for diagnosis and management; however, if there are no primary lesions, then other causes of pruritus should be ruled out before making the assumption that the pruritus is a result of the patient's kidney disease (refer to the BCPRA Management of Pruritus in Patients with CKD (Management of Pruritus In Patients With Chronic Kidney Disease 2017). Initial treatment measures are directed towards the management of dry skin since this is the most common reason for pruritus in CKD. These measures include: modifications in bathing habits (use fragrance-free soap, limit use of soap to axillae and groin/perineum, and avoid excessive bathing or bathing with hot water), avoiding wearing rough clothing such as wool over itchy areas, using a mild detergent and rinsing laundry well, keeping fingernails short and clean, and keeping the home cool and humid. Topical fragrance-free emollients are recommended first-line. Capsaicin 0.025% cream or pramoxine 1% cream or lotion may be considered. If the above measures are ineffective, then oral agents could be prescribed. Antihistamines such as hydroxyzine or diphenhydramine have been used conventionally. If the pruritus persists, then less conventional agents such as gabapentin, pregabalin, sertraline, or doxepin could be trialed. In patients who are resistant to both topical and oral agents, UVB therapy has been successfully utilized in some patients; however, a referral to a dermatologist is usually required for this type of treatment (Management of Pruritus In Patients With Chronic Kidney Disease 2017; Patient Teaching Tool – Itchy Skin (Pruritus) 2017).

4.8.8 Constipation

Constipation is a common problem in patients with kidney disease due to a number of factors including decreased fiber and fluid intake from dietary restrictions, being physically inactive, and taking medications, e.g. oral iron or phosphate binders such as calcium carbonate or calcium acetate, that may be constipating. Patients should try to maintain regular bowel movements with the goal of having one bowel movement every 1–2 days. This is especially important in peritoneal dialysis patients as constipation may impact a patient's dialysis therapy negatively. Non-pharmacological strategies should be trialed first and include increased fibre and fluid intake if possible within a patient's diet and fluid restriction allowance, participation in physical activities, and going to the washroom as soon as the urge for a bowel movement is

felt (refer to BCPRA Constipation Patient Teaching Tool) (Patient Teaching Tool – Constipation 2017). For chronic constipation, regular lactulose or polyethylene glycol (PEG) 3350 without electrolytes is recommended with or without docusate depending on the stool consistency. If the patient is complaining of hard stools, then docusate could be added. If the patient has not had a bowel movement in 3 days, then lactulose or PEG 3350 could be ordered if the patient is not already on any laxatives or if the patient is already on these medications, then the doses could be increased. In some cases, initial use of a stimulant laxative such as sennosides or bisacodyl may be required. Rectal therapies, i.e. an enema or a suppository, or manual disimpaction may be considered if constipation persists beyond 7 days. Fiber-containing laxatives are generally used with caution in patients with CKD due to the need for adequate water intake. Any laxatives that contain magnesium, phosphate or potassium should also be avoided (Management of Constipation In Patients With Chronic Kidney Disease 2017).

4.8.9 Muscle Cramps

Muscle cramps are involuntary muscle contractions that are associated with severe pain. They generally occur more frequently in dialysis patients and in particular, conventional hemodialysis patients who dialyze three times a week for 4 h each run. The exact cause of muscle cramps is unknown. It is felt to be related to nerve conduction more so than the muscles themselves. There are a number of factors that may contribute to the development of this complication including volume contraction, hypotension, changes in plasma osmolality, hyponatremia, tissue hypoxia, hypomagnesemia, carnitine deficiency and elevated serum leptin (Raymond and Wazny 2011). The most common reason for the development of muscle cramps is usually excessive fluid removal within the short time period that patients are on hemodialysis is. As with the previous symptoms, non-renal causes of muscle cramps should be ruled out prior to the initiation of therapy. Non-pharmacological strategies such as daily stretching, getting up and walking around if sitting for long periods, light exercise before going to bed, etc. should be trialed first and if ineffective, the prescription of pharmacologic agents could be considered (see the BCPRA Management of Muscle Cramps in Patients with CKD algorithm for a full list of non-pharmacological strategies) (Management of Muscle Cramps In Patients With Chronic Kidney Disease 2017). Quinine, which has previously been prescribed for the treatment of muscle cramps, is no longer recommended due to a black box warning on this drug. It has been reported to cause severe adverse effects including cardiac arrhythmias, thrombocytopenia, and hypersensitivity reactions (Stevens-Johnson Syndrome) that were life-threatening or required patient hospitalization. Vitamin E 400 units orally daily could be considered and if ineffective, then gabapentin could be trialed and uptitrated to achieve symptom relief (Raymond and Wazny 2011; Management of Muscle Cramps In Patients With Chronic Kidney Disease 2017).

4.8.10 Restless Legs Syndrome

Restless legs syndrome (RLS) is a condition where an unpleasant achy, creeping, crawling, or itching sensations of the lower legs may be felt. These uncomfortable feelings cause the person to want to move to try to stop the discomfort (Novak et al. 2015; Patient Teaching Tool – Restless Legs Syndrome 2017). Formal RLS diagnostic criteria include:

- An overwhelming urge to move the legs often, which may be accompanied by unpleasant sensations in the legs.
- These movements or sensations begin or worsen during rest or inactivity.
- These movements or sensations partially or totally dissipate, usually temporarily, by movement.
- These movements or sensations are worse in the evening or at night than during the day.
- These symptoms are not caused by another primary medical or behavioral condition such as myalgia, venous stasis, leg cramps, arthritis, habitual foot-tapping, etc.

The exact pathophysiology of RLS is unknown. From studies of animals and humans, it is hypothesized that disorders of brain iron metabolism and dopamine neurotransmission may be possible mechanisms. Iron deficiency should be suspected in individuals with a more acute presentation of RLS (Novak et al. 2015).

As with all the previous symptoms, proper assessment and treatment of contributing factors should be undertaken before the implementation of medical therapy. Iron deficiency should be treated and medications that may exacerbate RLS should be stopped or substituted if possible. Non-pharmacological strategies for the management of RLS include avoiding or limiting caffeine, alcohol and nicotine consumption, planning for breaks or periods of time to walk around and stretch, daily physical activity, etc. (refer to BCPRA Management of Restless Leg Syndrome in Patient with CKD (Management of Restless Leg Syndrome In Patients With Chronic Kidney Disease 2017) as well as the BCPRA Patient Teaching Tool for RLS (Patient Teaching Tool – Restless Legs Syndrome 2017) for a full list of recommendations). If a patient has intermittent RLS, levodopa/carbidopa (Sinemet®) 100/25 mg 0.5 tablet orally prn prior to anticipated RLS event could be prescribed and uptitrated based on symptom relief up to 200/50 mg orally daily. If breakthrough cramps occur in the evening, then a controlled release formulation could be considered. For daily RLS, dopamine agonists such as ropinirole 0.25 mg orally 2 hours prior to bedtime may be a better option. If the patient has RLS and concomitant pain, leg cramps or pruritus, then gabapentin 100 mg orally hs or pregabalin 25 mg orally hs could be trialed (Management of Restless Leg Syndrome In Patients With Chronic Kidney Disease 2017).

4.9 Pharmacist as a Team Member

The pharmacist is an integral part of the renal patient's journey. Interactions with the individual patient can provide understanding of the benefits and pitfalls of medication and how best to self-manage symptoms. It is with dialogue that we can create a best possible medication history and use this 'truth" to assess the patient. Moreover, we are well positioned to overcome barriers to adherence such as cost, dosage format, and time of day, or resolving misconceptions that may limit use.

We have a responsibility to manage a patient's medications for best outcomes and to advocate on their behalf. We need to liaise with other health care providers to coordinate care. Renal patients undergo transitions frequently. They are often seen in multiple clinics and tend to be admitted to acute care more than a comparable non-renal patient. Communicating the medication list effectively to the next provider of care is fundamentally important. As experts in dose and renal specifics of each drug, we can help avoid many unintended consequences. For instance, should a patient with chronic kidney disease contract the flu and subsequently become volume depleted, there is a risk of acute kidney failure. To mitigate that risk, we need to make the patient and others aware of sick day management through avoidance of certain medications. Further, we must continue to educate our hospital colleagues about the risks of contrast dye and aminoglycoside use. With respect to dose, we should observe the recommended ceiling doses for each stage of kidney disease and use alternatives to medications that accumulate active or toxic metabolites. We must always navigate to best kidney health.

The nephrology pharmacist is not always available to each patient. To this end, time must be spent creating policies, procedures and clinical pathways to support best outcomes. While it is necessary to individualize therapy for the complex renal patient, it is essential to standardize drug therapy to best available evidence where such evidence exists. If it is demonstrated that the patient is better served deviating from the standard care, therapy can be individualized to address the care gap. For instance, if an anemia management protocol directs 125 mg of intravenous iron gluconate to be given monthly, yet the patient is hypotensive and/or experiences back pain with that dose, a different dose or drug could be considered. Using a half or a quarter of that dose will likely alleviate those symptoms or switching to another injectable iron may work. The individualized approach should always be made in the context of the local realities of cost, availability and policy. Individualization may be necessary for many reasons including drug interactions, tolerability (as above), affordability, patient preference, and patient factors (cognition, comorbid conditions, contraindications).

4.9.1 Pharmacists Role

The literature outlining a nephrology pharmacists' role is drawn from several countries. First, the UK Renal Pharmacists Group was the first to outline a list of duties required for good care (UK Renal Pharmacy Group 2004). Secondly, an American group contributed their thoughts on duties but also on the value pharmacists bring to the patient and organization (Joy et al. 2005; Manley and Carroll 2002; Pai et al. 2009). More recently, Raymond and Wazny published on their Manitoba pharmacist group standards of clinical practice for renal pharmacists (Raymond et al. 2013).

Taken together, the scope of the role is more clearly defined than Kaboli's work and is complementary to his five patient outcomes that improve patient outcomes (Kaboli et al. 2006). Kaboli et al. identified that the following clinical pharmacist services resulted in improved care with no evidence of harm. Interacting with the health care team on patient rounds, interviewing patients, reconciling medications and providing patient discharge counselling and follow up all improved outcomes (Kaboli et al. 2006).

Focussing on each paper, one can see the various activities are more similar between them than different. In the UK standards, the following relevant major statements are made although focuses on dialysis patients) (UK Renal Pharmacy Group 2004):

1. The renal pharmacist will review each hospital dialysis patients' prescriptions at least once every 6 months to ensure that all aspects of each prescribed drug is appropriate for that individual.
2. The renal pharmacist will review each non-hospital dialysis patients' prescriptions at least once every 6 months to ensure that all aspects of each prescribed drug is appropriate for that individual.
3. The renal pharmacist will review an individual outpatients' prescriptions to ensure that all aspects of each prescribed drug is appropriate for that individual when that patient is referred by a healthcare professional
4. The renal pharmacist will ensure that all renal outpatients have access to medication counselling.
5. The renal pharmacist will contribute to the weekday planned discharge of patients.
6. The renal pharmacist will use their experience, in conjunction with the evidence-base, to advise on each patient specific request for information about drugs in renal failure or dialysis patients.
7. The renal pharmacist will contribute to or review all new, local, renal protocols, polices and guidelines to ensure that recommended medicine use is safe, effective and economical.
8. All renal pharmacists should have at least 2 years post-residency as a hospital clinical pharmacist. Renal pharmacists will have a personal development plan that addresses their clinical development.

The role of the clinical pharmacist in chronic kidney disease is well supported by a number of studies and a recent paper from the United States highlighted the issue of potentially inappropriate medications in the elderly on dialysis (Gallieni and Cancarini 2015). In it, the authors outline a list of target medications with the most problematic being analgesics, endocrine agents, cardiovascular drugs and oral anticoagulants.

While a nephrologist might incorporate such information into his or her practice, such identification and resolution is often the result of a clinical pharmacist's review. The integration of the patient status (e.g. age, comorbidities, drugs) is within the clinical pharmacy scope while it is not the domain of the pharmacy technician. An important aspect of the pharmacist's review outside of the BPMH is the falls risk review. Such a review is not prompted by a scheduled review but by a fall or identification of a falls risk by a nurse.

4.9.2 Medication Reconciliation

Some studies pre-date the introduction of the term of medication reconciliation as a process. However, obtaining an accurate medication history to assess and optimize medications has been a core function of a clinical pharmacist for some time. The evidence of benefit reconciling medications is found in pharmacist-led work and has resulted in accreditation bodies adopting the process as a required organizational practice. Pharmacists should not be should be encouraged not to meet a minimally acceptable practice but should focus on maximizing the core improvements that arise from the work. Reconciling renal patients' medications takes time and cognitive skill. More recently, some pharmacists are utilizing a clinical pharmacy technician to complete best possible medication histories. Seen as "pharmacist extenders", these technicians seek the truth so that the pharmacist may assess the truth. Such a team is more efficient in both time and money for the work produced.

4.9.3 Deprescribing

Deprescribing is the process of intentionally stopping a medication or reducing its dose to improve the person's health or reduce the risk of adverse side effects (Reeve et al. 2015; Thompson and Farrell 2013). Deprescribing is usually done because the drug may be causing harm, may no longer be helping the patient, or may be inappropriate for the individual patient's current situation. For the renal pharmacist, there are three opportune times to consider deprescribing: when a patient is deemed to be at a falls risk or has fallen, at the point of reconciling medications after review, and when a patient transitions to a palliative approach. The falls risk review identifies potential anti-hypertensives, hypoglycemic and CNS active agents that can be stopped, for example. Likewise, any number of discrepancies identifying drug

related problems at reconciliation result in inappropriate drugs being stopped or reduced. Finally, the palliative approach likely will result in longer term outcome medications being discontinued, such as bisphosphonates and HMG-CoA reductase inhibitors (“statins”). When done properly, though, a thorough medication review can incorporate all three deprescribing opportunities.

4.9.4 Valuing the Clinical Pharmacist

Many publications outline the inherent value of a clinical pharmacist and some further define how a pharmacist can be most valuable to improving patient outcomes with no evidence of harms. Clinically, if pharmacists interact with the health care team on patient rounds, interview patients, reconcile medications, provide patient discharge counselling and follow-up (as outpatients), patient outcomes are improved (Kaboli et al. 2006) . Other researchers concluded “Receipt of integrated pharmacy services was associated with lower rates of death and hospitalization in hemodialysis patients with concurrent Medicare and Medicaid eligibility” (Weinhandl et al. 2013). These authors identified by intention to treat analysis that patients were 8% less likely to die, had 2% fewer hospitalizations and 6% fewer days.” As treated analysis” demonstrated 21% less likely to die, 7% fewer admissions and 14% fewer days in hospital.

Perhaps more interestingly from a finance and cost justification perspective, it has been estimated that for every dollar spent on a pharmacist, $4.81 was achieved in reduced cost or other benefits (Perez et al. 2009). This result has been more recently reviewed and given an upper range ratio of $1:$25 depending on the service (Touchette et al. 2014). More specifically for a transplant clinical pharmacist, the cost benefit ratio has been determined to be $1:$4.16 (for every dollar spent on a pharmacist, $4.16 was avoided (Chisholm et al. 2000). Yet another author also found that spending $1 on pharmaceutical care for end stage renal disease patients yields $3.98 in health care system savings in avoided hospitalizations, reduced medications and other drug related problems (Manley et al. 2005).

It is clear that not only do patients benefit from improved health outcomes by having a clinical pharmacist on their team; the health system costs are also reduced or at least better spent if budgets remain the same.

Renal pharmacists add value to patient care while delivering better value for money than their salaries. Pharmacists are almost uniquely positioned to provide greater savings to the system than their salaries by a 4:1 margin.

4.9.5 Staffing Ratios

The literature does not provide good guidance to the renal team to determine a pharmacist to patient ratio to provide good pharmacist care. Unpublished examples from British Columbia and Manitoba, Canada do provide some estimates. Funding mod-

els in each province for clinic patients with eGFR below 30 mL/min not yet on dialysis suggest one pharmacist per 500 patients. This ratio, however, does not take into account the inclusion of a pharmacy technician creating best possible medication histories (BPMH). However, as BPMH is only one component to clinical pharmacist care, one could argue the ratio should still hold true. Finding the peak benefit to cost ratio of pharmacists has not been reported in the literature as such. However, a detailed review of interventions that improve patient outcomes, published standards of care for renal pharmacists and funding models reveal that even a generous pharmacist to patient staffing could still be cost effective.

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Chapter 5
Dialysis

Timothy Nguyen, A. Mary Vilay, Neeta Bahal O'Mara, and Rebecca Maxson

Advanced Clinical Pharmacy *- Research, Development and Practical Applications: "dose adjustments and other considerations in dialysis – including types of dialysis, how these differ and affect PK. As well as understanding the inefficiencies of dialysis and the impact on patient's life".*

Abstract Dialysis is a life-saving treatment option for patients with kidney failure. There are several common dialysis modalities commonly used in clinical practice such as hemodialysis (HD), peritoneal (PD), and continuous renal replacement therapy (CRRT) (Sowinski KM, Churchwell MD, Decker BS (2017) Hemodialysis and peritoneal Dialysis. In: Dipiro JT, Talbert RL, Yee GC et al (eds) Pharmacotherapy. A pathophysiologic approach (10 e). McGraw Hill Education, New York). Dialysis is the transfer of uremic solutes from blood to an extracorporeal fluid (dialysate) by diffusion across a semi-permeable membrane (Sowinski KM, Churchwell MD, Decker BS (2017) Hemodialysis and peritoneal Dialysis. In: Dipiro JT, Talbert RL, Yee GC et al (eds) Pharmacotherapy. A pathophysiologic approach (10 e). McGraw Hill Education, New York). This can be accomplished by pumping blood through a

T. Nguyen (✉)
Arnold & Marie Schwartz College of Pharmacy and Health Sciences, Long Island University, Brooklyn, NY, USA
e-mail: timothy.nguyen@liu.edu

A. M. Vilay
University of New Mexico College of Pharmacy, Albuquerque, NM, USA
e-mail: mvilay@salud.unm.edu

N. B. O'Mara
Coldstream Consulting, Skillman, NJ, USA

R. Maxson
Auburn University Harrison School of Pharmacy, Auburn, AL, USA
e-mail: maxsora@auburn.edu

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dialyzer containing a membrane (HD or CRRT) or by instilling dialysate into the peritoneal cavity and using the peritoneum as a membrane (PD). Solute removal via HD is relatively efficient and can be done intermittently (typically 3 times per week), whereas PD is less efficient and is usually required for 12–24 h every day. Continuous renal replacement therapy is used to treat acute kidney injury (AKI) in critically ill and hemodynamically unstable patients.

There is conflicting information regarding survival differences between PD and HD; however, some reports show no significant difference in survival between the two modalities and it also depends on a number of factors (Sowinski KM, Churchwell MD, Decker BS (2017) Hemodialysis and peritoneal dialysis. In: Dipiro JT, Talbert RL, Yee GC et al (eds) Pharmacotherapy. A pathophysiologic approach (10 e). McGraw Hill Education, New York; Vonesh EF, Snyder JJ, Foley RN, Collins AJ Kidney Int 66:2389–2401, 2004; Miskulin DC, Meyer KB, Athienites NV et al Am J Kidney Dis 39:324–336, 2002). The direct comparison of PD and HD is difficult due to the differences in the nature of the various procedures involved and the complex relationship between patient factors and outcomes (Vonesh EF, Snyder JJ, Foley RN, Collins AJ Kidney Int 66:2389–2401, 2004; Miskulin DC, Meyer KB, Athienites NV et al Am J Kidney Dis 39:324–336, 2002).

Pharmacotherapy regimens are often complicated because many of these patients have multiple comorbidities (Sowinski KM, Churchwell MD, Decker BS (2017) Hemodialysis and peritoneal Dialysis. In: Dipiro JT, Talbert RL, Yee GC et al (eds) Pharmacotherapy. A pathophysiologic approach (10 e). McGraw Hill Education, New York; Vonesh EF, Snyder JJ, Foley RN, Collins AJ Kidney Int 66:2389–2401, 2004; Miskulin DC, Meyer KB, Athienites NV et al Am J Kidney Dis 39:324–336, 2002). In addition, the type of dialysis procedure (HD vs. PD vs. CRRT) have variable effects on the disposition of these medications. Kidney failure patients also have multiple repetitive hospitalizations due to recurrent complications (Possidente CJ, Bailie GR, Hood VL Am J Health-Syst Pharm 56:1961–1964, 1999). On average dialysis patients receive more medications to manage kidney related complications (Possidente CJ, Bailie GR, Hood VL Am J Health-Syst Pharm 56:1961–1964, 1999). Therefore, the number of medication-related problem (MRP) in the dialysis population is large and along with dialysis related procedures lead to decrease in quality of life (Grabe DW, Low CL, Bailie GR, Eisele G Clin Nephrol 47:117–121, 1997).

Keywords Dialysis · Haemodialysis · Pharmacokinetics · Drug clearance

5.1 Hemodialysis

Hemodialysis is an extracorporeal renal replacement therapy used predominantly to treat patients with chronic kidney disease (CKD). However, HD can be used to manage patients with AKI or medication overdoses (Palevsky et al. 2008). Hemodialysis

is capable of correcting acid/base imbalances, some electrolyte disorders, fluid overload, and clearing uremic solutes. Hemodialysis is also effective in treating severe overdoses with select agents, such as lithium, (Decker et al. 2015) salicylates (Juurlink et al. 2015) and methanol (Robert et al. 2015).

5.1.1 Principles of Hemodialysis

Hemodialysis involves filtering solutes and water in blood across a semipermeable membrane, the dialyzer (Fig. 5.1) (Tolwani 2012). Depending upon the dialyzer manufacturer, the membranes are made from such biocompatible materials as cellulose acetate or polysulfone. The membranes have a microporous structure allow the diffusion of small molecular weight from molecules and water from the blood to the dialysate. Solute clearance during HD may occur through adsorption, diffusion, and convection. During adsorption, solutes adhere to the HD tubing and/or dialyzer contributing to solute clearance. Through diffusion, solutes move from an area of

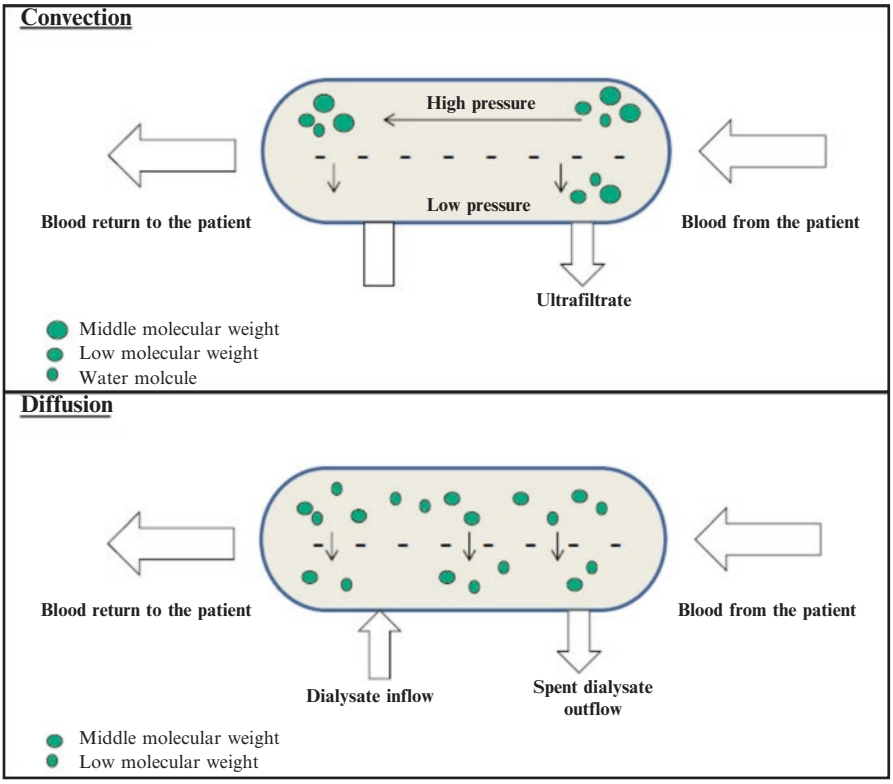

Fig. 5.1 Transport of solutes across a semipermeable membrane. (Tolwani 2012)

high concentration to an area of low concentration (Fig. 5.1) (Tolwani 2012). During HD, small molecules such as urea, creatinine, and some electrolytes are removed by diffusion (Sowinski et al. 2017). Convection occurs due to the ultrafiltration of water from the blood compartment (Fig. 5.1). Dissolved solutes will move with water across the semipermeable membrane as long as the solutes are smaller than the dialyzer pores. Convection is effective at clearing larger molecules such as beta-2 microglobulin, a middle molecular weight compound (Locatelli et al. 2018; Blankestijn et al. 2010).

The convective clearance achieved with a dialyzer determines whether the dialyzer is classified as a low-flux versus high-flux dialyzer. The large majority of HD treatments in the United States today are being conducted using high-flux dialyzers (Blankestijn et al. 2010). High-flux dialyzers have larger pores and ultrafiltration coefficients (Kuf) >15 mL/h/mm Hg (Eknoyan et al. 2002). Therefore, high-flux dialyzers result in enhanced clearance, particularly of middle-to-large molecular weight compounds. Another advantage of high-flux dialyzers is that they are more bio-compatible and will activate complement to a lesser degree contributing to decreased inflammation and oxidative stress (Del Vecchio et al. 2011). Enhanced solute clearance can also be achieved by modifying the dialysis prescription. Hemodiafiltration achieves higher convective clearance than HD while still achieving some diffusive clearance. The increased convective clearance results in increased removal of middle molecules such as peptides and low-molecular weight proteins (Locatelli et al. 2018; Blankestijn et al. 2010).

Considerable clearance can be achieved in a relatively short period (e.g., 3–5 h) with HD, due to the high rates of blood flow, dialysate flow, and ultrafiltration rates used. The high clearance rates allow for HD to be provided intermittently (e.g., 3 times a week). However, the rapid clearances achieved may also contribute to dialysis disequilibrium syndrome, intradialytic hypotension, and muscle cramping (Sowinski et al. 2017). Patients undergoing HD are also at increased risk of infections and thrombosis (Sowinski et al. 2017). Given the highly technical nature of HD, it is usually be performed in center at a dialysis center or other healthcare facility, although recently there are initiatives for certain types of home HD as well.

5.2 Peritoneal Dialysis

The use of the peritoneum as a renal replacement therapy has been described since the early 1900's (Sowinski et al. 2017; Maxwell et al. 1959). In fact, as early as 1919, the principle of urea diffusion from the blood into the peritoneal cavity was described. The first attempt at PD in humans occurred during World War II, when frustrations over thousands of soldiers dying of AKI prompted investigators to use peritoneal irrigation as a method to prolong survival in soldiers with kidney injury. In its primitive form, PD was performed using abdominal metal trochars that were inserted and left in place for hours while the peritoneal cavity was continually irrigated. Since then, PD has evolved into the form of renal replacement therapy that we know today (Sowinski et al. 2017).

5.2.1 *Principles of PD Modalities*

The peritoneal cavity is defined as the space between the parietal peritoneum (the peritoneum that surrounds the abdominal wall) and visceral peritoneum (the peritoneum that surrounds the internal organs) (Sowinski et al. 2017; Maxwell et al. 1959). Peritoneal dialysis involves the instillation of a hypertonic dialysate solution into the peritoneum through a catheter (Fig. 5.2. **Peritoneal Dialysis**) (https://www.niddk.nih.gov/health-information/kidney-disease/kidney-failure/peritoneal-dialysis 2019). The solution remains in the peritoneum for a pre-specified period of time. During this time, smaller solutes and water cross through the peritoneal membrane into the hypertonic dialysate solution. The fluid is then drained through the catheter and the process is repeated. Normally, the peritoneum cavity contains a small amount of fluid, but when used for peritoneal dialysis, it can accommodate larger amount of fluid. The very vascular perioneal area provides an excellent membrane for diffusion and convection to filter water, electrolytes and toxins from the peritoneal blood supply into the peritoneal cavity.

There are two types of PD, continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD) (Sowinski et al. 2017). While both methods may take advantage of extended "dwell times", the time the dialysate remains in the peritoneum, the number of exchanges and how exchanges treatments are performed are different. In CAPD, fluid is instilled in the peritoneum and subsequently drained periodically throughout the day. The dialysis fluid is exchanged manually using

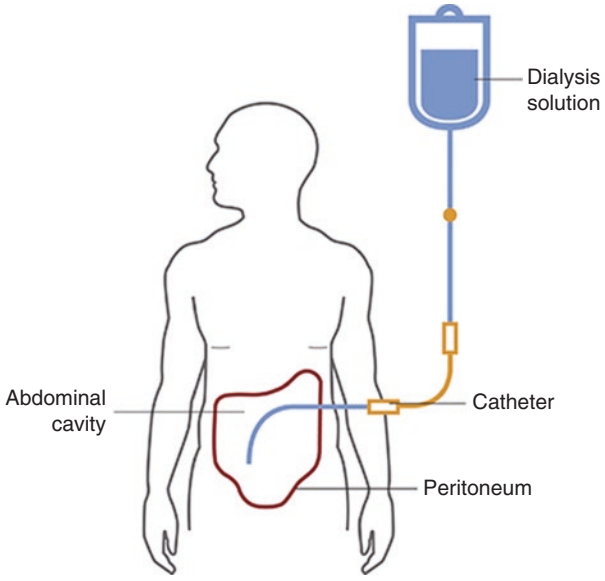

Fig. 5.2 Peritoneal dialysis (https://www.niddk.nih.gov/health-information/kidney-disease/kidney-failure/peritoneal-dialysis 2019)

gravity to drain and fill the abdomen. For APD, a machine or cycler delivers and then drains the dialysate into the peritoneum, usually during the overnight hours.

The PD catheter is needed for bidirectional flow of dialysate. Peritonitis is the leading complication of PD, amongst other complications such as mechanical and medical complications. Solute clearance, fluid removal, and clinical assessment help determine the adequacy of PD. Some examples of advantages and disadvantages of PD include: slow ultrafiltration rate, better preservation of residual renal function, convenient, freedom from in-center facility, less complications; however, risk of peritonitis, inadequate ultrafiltration, and patient-related factor (Sowinski et al. 2017).

5.3 Continuous Renal Replacement Therapy

Continuous renal replacement therapy (CRRT) and prolonged intermittent renal replacement therapy (PIRRT) have emerged for providing renal support in hemodynamically unstable AKI patients. Both modalities are based upon the principles of HD.

5.3.1 Principles of CRRT and PIRRT

As shown in Figs. 5.3, 5.4, 5.5, 5.6 and 5.7, CRRT is an all-encompassing term that describes slow continuous ultrafiltration (SCUF), continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD) and continuous venovenous hemodiafiltration (CVVHDF). Traditionally, all forms of CRRT involve 24-h renal replacement therapy with slow blood and effluent flow rates, specialized replacement fluid solutions, requirement for continuous anticoagulation and intense nursing times (Bellomo et al. 1996).

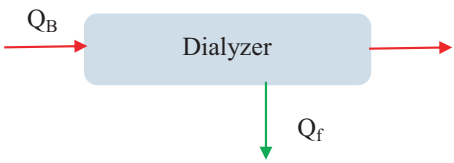

Fig. 5.3 SCUF

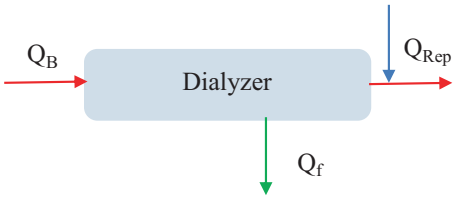

Fig. 5.4 CVVH – Post dilution

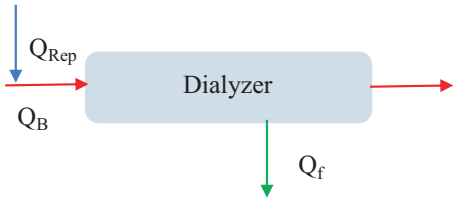

Fig. 5.5 CVVH – Pre dilution

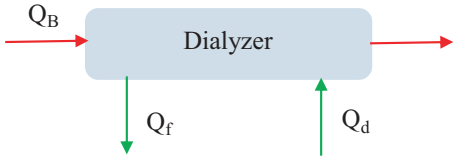

Fig. 5.6 CVVHD

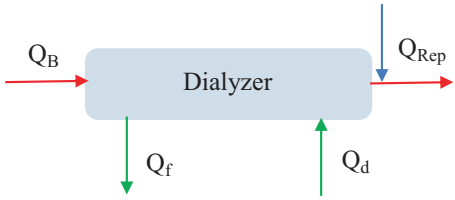

Fig. 5.7 CVVHDF

PIRRT and other associated terms (Table 5.1) are used to refer to a hybrid of HD and CRRT which provides RRT for a prolonged time on an intermittent basis (Edrees et al. 2016). PIRRT is generally performed for 6–8 h with a 200 mL/min blood flow rate and 300 mL/min dialysis flow rate (Kumar et al. 2000). Thus, PIRRT is intermittent like HD which allows time for procedures and physical therapy with gentler fluid removal similar to CRRT (Bailie and Mason 2018). The advantages of PIRRT compared to CRRT include reduced costs from expensive replacement fluid solutions, no requirement for a separate RRT machine from the HD machine, and allows time off of therapy for procedures and physical therapy (Edrees et al. 2016).

Like HD, PIRRT and CRRT remove fluid and solutes (including medications) using both convection and diffusion (Fig. 5.1) (Tolwani 2012; Bellomo et al. 1996). The impact of convection versus diffusion on solute removal varies depending on the specific modality used (Table 5.2).

5.3.1.1 Pharmacokinetics

A major consideration in dialysis is renal clearance. Dialysis modality results in extracorporeal clearance of small molecule drugs. The extent to which dialysis removes a particular drug from plasma is dependent on its bioavailability, volume of distribution (Vd), water solubility, protein binding, molecular weight, and drug metabolism/renal elimination (Sowinski et al. 2017). Bioavailability (F) refers to

Table 5.1 Various terms for PIRRT used in the literature. (Kumar et al. 2000)

Acronym	Description
S-HDF	Sustained hemodiafiltration
SLED	Sustained low-efficiency dialysis
AVVH	Accelerated venovenous hemofiltration
ED	Extended dialysis
EDD	Extended daily dialysis
E-HFD	Extended high-flux hemodialysis
SLEDD-f	Sustained low-efficiency daily diafiltration

Table 5.2 Comparison of different modes of dialysis. (Edrees et al. 2016)

Parameter	SCUF	CVVH	CVVHD	CVVHDF	PIRRT
Duration	Continuous				6–8 hs
Dialysate flow (mL/min)	N/A	N/A	10–30	20–40	100–300
Blood flow (mL/min)	50–200	50–200	50–200	100–200	160–200
Convection	Low	High	Low	High	Depends[a]
Diffusion	Low	Low	High	High	Depends[a]

[a]small number of pharmacokinetic studies have shown higher drug clearance with PIRRT than HD with a meta-analysis showing higher clearance with PIRRT than CRRT depending on blood flow, dialysis flow and filter used (Kumar et al. 2000)

the amount of drug that reaches the blood stream. There are many factors that can influences the F of a drug and that can interfere with its ability to be dialyzed. Drugs with large Vd can distribute widely throughout tissues with small amounts in the blood and minimally dialyzed. In patients with kidney disease and the presence of co-morbid condition such as hepatic dysfunction, altered Vd is observed. Hypoalbuminemia can result in increased free fraction of highly protein-bound drugs, therefore enhance drug clearance (Sowinski et al. 2017; Meijers et al. 2008). The movement of drugs during dialysis procedure is mostly related to the size of these molecules, protein binding property, and the size of the membrane. Smaller molecular weight drugs may pass through the membrane more easily compared to larger molecular weight drugs. Dialysis plays significant role in drugs elimination in kidney failure patients in which both parent compound and metabolites can accumulate. The marked decrease in GFR results in an increase in half-life of many drugs (Sowinski et al. 2017). Drugs can also accumulate with repeated dosing.

5.4 Hemodialysis

Of the four pharmacokinetics (PK) processes, drug absorption, distribution, metabolism, and elimination, HD has the biggest impact on drug elimination. The greatest challenge with drug PK during HD is the potential of periods of very low clearance

Table 5.3 Drugs and properties affecting drug clearance (Sowinski et al. 2017), (Eknoyan et al. 2002), (Kumar et al. 2000; Bailie and Mason 2018; Lexicomp Online 2019; Micromedex® (electronic version 2019)

Molecular size
Protein binding
Volume of distribution
Water solubility

interspersed (when the patient is not actively receiving HD) with intervals of notably enhanced clearance (during the actual HD procedure). Drug dosing during HD requires consideration of drug characteristics (Table 5.3), dialysis characteristics such as blood and dialysate flow, and patient factors such as amount of residual renal function. Whether a drug is removed by HD is influenced by the drug's molecular weight, plasma protein binding, volume of distribution, and water solubility (Table 5.3) (Sowinski et al. 2017). Often it is difficult to predict whether a drug will be removed during HD based on its physicochemical properties alone. A number of tertiary drug information resources provide data on whether a drug is dialyzable (Bailie and Mason 2018; Lexicomp Online 2019; Micromedex® (electronic version) 2019). When consulting drug information resources, it is important to note the type of dialyzer (low flux versus high flux) studied. The differences in pore size between low-flux and high-flux dialyzers will greatly impact the clearance of drugs (Sowinski et al. 2017).

Hemodialysis clearance is considered clinically significant when it contributes to at least 30% of the total drug clearance (Sowinski et al. 2017). In this situation, an increase in drug dosage to account for removal by dialysis may be warranted. Additionally, if HD clearance is considerable, a supplemental dose post-HD and/or delaying the timing of drug administration until after HD, particularly for drugs that are dosed once daily is recommended (Sowinski et al. 2017; Eknoyan et al. 2002; Bailie and Mason 2018; Lexicomp Online 2019; Micromedex® (electronic version) 2019).

Drug dosing recommendations taking into account dialysis clearance and the need for supplemental doses can also be found in tertiary drug information resources (Bailie and Mason 2018; Lexicomp Online 2019; Micromedex® (electronic version) 2019). However, the dosing recommendations are generally based on data for HD performed three times a week for 3–5 h sessions. If HD is provided at an increased frequency and/or for prolonged time intervals, as is seen in the setting of AKI, (Palevsky et al. 2008) the drug dosing recommendations found in tertiary drug information resources may result in drug under-dosing (Lexicomp Online 2019; Micromedex® (electronic version) 2019). Since many variable affect HD drug clearance, therapeutic drug monitoring should be used to guide therapy, when possible.

5.5 Peritoneal Dialysis

The effects of PD on drug PKs are difficult to predict. Factors which affect drug dialyzability in patients receiving PD include drug protein binding, drug volume of distribution, drug molecular size, drug degree of hypophilicity or lipophilicity, peritoneal membrane permeability, surface area, blood flow, dialysate dwell time, and dialysate glucose concentration (Hirata and Kadowaki 2012). Compared to HD (e.g., flow rate is usually high, greater than 350 mL/min or higher), drug clearance is much slower in PD, with an estimated maximum clearance rate of 4 mL/minute to 7 mL/minute, even for low molecular weight medications (Sowinski et al. 2017). Because the rate of drug clearance by PD is low, often, the same drug dosing regimens as those used in patients with very low creatinine clearances (e.g., 5 mL/minute to 10 mL/minute) can be employed. In general, in a euvolemic patient, the loading dose of a drug during PD should be similar to the loading doses used in patients with normal renal function. However, subsequent dosing may need to be adjusted, based on the characteristics of the medication.

5.6 Continuous Renal Replacement Therapy

In general drugs with a low volume of distribution (Vd, <1 L/kg), low molecular weight, low plasma protein binding (PPB, <80%) and high renal clearance are easily removed by RRT (Choi et al. 2010; Bogard et al. 2011). However, standard PK data derived from healthy patients is altered in critically ill patients. Bauer and colleagues (Bauer et al. 2012) reported a larger Vd and lower PPB for piperacillin-tazobactam in critically ill patients versus noncritically ill patients. Early on, patients with sepsis typically will have larger Vd due to third spacing, decreased plasma albumin and other alterations (Bauer et al. 2012). The SAFE study reported that PPB is also altered in ICU patients due to decreases in plasma albumin (SAFE Study Investigators 2006). All of these PK changes plus a decline in renal elimination from AKI with or without RRT makes dosing in critically ill patients very challenging.

Despite changes in PK and renal elimination, many of the medications administered to critically ill patients are titrated to effect (e.g., vasopressors, inotropes, sedating medications) and as such are relatively easily dosed. Antibiotics however are an exception where PK and elimination changes can drastically change the dose needed to meet the necessary pharmacodynamic target. Despite the difficulty in antibiotic dosing in the setting of CRRT and PIRRT, there remains limited data on appropriate dosing strategies. According to the "Hour-1 Surviving Sepsis Campaign Bundle of Care", empiric broad-spectrum antibiotics should be started as soon as sepsis is identified (Levy et al. 2018). Early empiric broad-spectrum antibiotics when dosed appropriately directly improves the mortality rate of patients with sepsis.

Martinez and colleagues (Martinez et al. 2012) recommend several strategies to maximize the likelihood of therapeutic success with early empiric antibiotics including, high drug concentrations with first exposure such that susceptible and resistant bacteria are killed followed by minimized drug exposure to reduce adverse drug reactions (Martinez et al. 2012). Studies have shown that adequately high doses with the first 3 days of therapy have a clinically and statistically significant positive impact on the probability of pathogen eradication (Martinez et al. 2012).

Initial loading doses can help improve achievement of PK/PD targets from the first dose (Ulldemolins et al. 2014). With CRRT and PIRRT, initiation of RRT in relation to antibiotic dosing should be considered. Either therapy will upset any achieved equilibrium which an additional loading dose at the start of RRT will theoretically mitigate (Ulldemolins et al. 2014). This concept is even more critical with PIRRT as timing of doses in relation to time on RRT must be considered. The concentration of time-dependent antibiotics may drop below the minimum inhibitory concentration during a prolonged RRT treatment (Edrees et al. 2016). After a sufficient loading dose and consideration of dose timing in relation to initiation and length of RRT, a maintenance regimen must be prescribed.

With the emphasis on adequate antimicrobial coverage in patients with sepsis, adequate loading doses are essential. Patients with AKI and/or RRT should receive the same loading doses as patients with AKI. When CRRT or PIRRT is initiated, additional loading doses may be needed to maintain adequate coverage at the site of infection. The subsequent maintenance doses should be chosen based upon the patient's current kidney function and RRT modality using primary literature and drug databases as guides. Finally, these patients should be closely monitored while on therapy for adverse drug reactions and changes to the patient's status, especially changes to RRT modality, dialysis prescription and kidney function.

5.7 Summary on Principles of Various Dialysis Modalities

Clinicians should consider characteristics of the drugs include molecular size, protein binding, volume of distribution, water solubility, and plasma clearances as these are vital important to the extent it is removed by dialysis.

5.7.1 Pharmacokinetics Considerations and Dosing in Dialysis

- Bioavailability (F)
- Volume of distribution (Vd)
- Protein binding
- Drug metabolism/renal elimination
- Other relevant factors: water solubility, molecular size

To summarize for drug dosing, if no information regarding dose adjustment in dialysis is available, one should assume that the GFR is very low. Although, some dialysis patients may have a little residual kidney functions left and so general considerations for dosing in these patients should be used. Drug dosage adjustments can be made by reducing the dose, increasing the interval or both.

5.8 Conclusion

Over the past many decades various dialysis modality has been the mainstay for treating kidney failure patients. Each dialysis modality has unique effect on medication property and medications use in patients dependent on dialysis, and can pose a challenge for clinicians.

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Chapter 6
Drug-Induced Nephrotoxicity

Adriano Max Moreira Reis

Abstract Drug-induced nephrotoxicity (DIN) is a relatively common adverse drug event that contributes to morbidity and increased healthcare utilisation. The phenotypes of DIN comprise acute kidney injury, tubular disorders, glomerular injury, and nephrolithiasis. The common risk factors of DIN include age, causal drug use, single and/or cumulative dosage, an underlying chronic kidney disease, comorbid diseases, and concurrent nephrotoxin exposures. Therefore, minimising the exposure to these risk factors may mitigate the development of DIN as it is an important and potentially modifiable renal adverse drug event. Identifying the medications that induce nephrotoxicity is essential in clinical practice. The clinical pharmacist, therefore, should understand and identify patients who are at the highest risk of developing DIN, implement the judicious use of nephrotoxic medications, and conduct frequent monitoring of such patients. The latter role of the pharmacist is especially important when a combination of nephrotoxic drugs is being used by a patient. For patients with confirmed DIN, the use of nephrotoxic drugs should be greatly avoided, to aid renal recovery and prevent recurrent DIN.

Keywords Nephrotoxicity · Adverse drug reactions · Kidney disease · Kidney injury · Nephrotoxic · Clinical pharmacy · Renal adverse drug event

6.1 Introduction

Inpatients and outpatients are exposed to a variety of potential nephrotoxic agents including prescribed medications, over-the-counter drugs, herbal drugs and diagnostic agents. Drug-induced nephrotoxicity (DIN) is a relatively common adverse drug event that contributes to morbidity and increased healthcare utilisation

A. M. M. Reis (✉)
Department of Pharmaceutical Products, Faculty of Pharmacy, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil
e-mail: amreis@ufmg.br

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(Perazella 2018). DIN is also known as drug-induced kidney disease or drug-induced kidney injury. It is more frequent in hospitalised patients, especially among patients in the intensive care unit (Perazella 2018; Kane-Gill and Goldstein 2015; Awdishu 2017; Bentley et al. 2010).

DIN is increasingly recognised as a significant contributor to kidney disease such as in acute kidney injury (AKI) and chronic kidney disease (CKD) (Perazella 2018; Mehta et al. 2015; Awdishu and Mehta 2017). Nephrotoxicity has a wide spectrum which is reflected by the damages observed in different nephron segments due to individual drug mechanisms. The primary strategy used to prevent DIN is avoiding the use of nephrotoxic drugs by patients with an increased risk of renal adverse drug event (Kane-Gill and Goldstein 2015; Awdishu 2017; Coulter 2018; Kane-Gill and Bauer 2017; Bartoli 2016). Therefore, it is essential that clinical pharmacists be aware of the potential nephrotoxic drugs, and be knowledgeable of the risk factors that increase renal vulnerability (Coulter 2018; Kane-Gill and Bauer 2017). Considering that often times, exposure to nephrotoxic drugs cannot be avoided, (Kane-Gill and Goldstein 2015), it is also essential that pharmacists recognise the interventions aimed at reducing the potential for developing nephrotoxicity.

This chapter will cover, in view of the clinical pharmacist, the clinical presentation, epidemiology, risk factors, mechanisms, diagnosis and management strategies for DIN.

6.2 Epidemiology of Drug-Induced Nephrotoxicity

Knowledge of the epidemiology of nephrotoxicity is predominantly based on inpatients, especially the epidemiology of drug-induced AKI (Perazella 2018; Awdishu 2017). The incidence and characteristics of outpatients or community-acquired DIN, has not been well described. However, the acquisition of data regarding the pharmacoepidemiology of DIN has become more important as patient care has shifted to the outpatient setting (Siew and Davenport 2015).

Nephrotoxicity is a significant concern in paediatrics, with 16% of hospitalised AKI events being primarily associated with exposure to a nephrotoxic medication (Awdishu and Mehta 2017; Joyce et al. 2017). The incidence of AKI in paediatric studies ranges from 7% to 25%, depending on the definition of AKI used, and the population under investigation (Glanzmann et al. 2016). Consequently, the true incidence of DIN has proven difficult to determine. Critically ill children are particularly susceptible to DIN. Drugs including antimicrobials, antineoplastic, non-steroidal anti-inflammatory drugs (NSAIDs) and calcineurin inhibitors, among others, have all been implicated in DIN in paediatric patients. However, it is difficult to determine the overall contribution of DIN in the paediatric intensive care unit, due to the case complexity of these critically ill patients (Joyce et al. 2017; Glanzmann et al. 2016; McWilliam et al. 2017; Faught et al. 2015). In addition, the incidence of AKI in the neonatal intensive care unit is unknown, even though many of the widely-used drugs in this unit, have exhibited well-recognised nephrotoxicity

in the adult population. Therefore, the role of these drugs in the onset of renal injury in neonates its challenging to recognize and remains unclear. The immaturity of renal functions in neonates is yet another challenge as well as a risk factor for renal injury in this population (Girardi et al. 2015; Girardi et al. 2017).

Data on DIN in the elderly, are mainly based on AKI and are mostly derived from hospital-based studies; the incidence of which ranges from 10% to 65% of all AKI episodes in the elderly. The incidence of AKI increases with age, as demonstrated in a study conducted using Medicare beneficiaries, with patients older than 80 years comprising 54% of all patients with an AKI-based hospitalisation (Khan et al. 2017). In the community setting, the incidence of DIN ranges from 19% to 54% of all AKI episodes in the elderly. Patients with this community-acquired AKI were found to be older than the individuals that did not develop AKI (Khan et al. 2017; Schissler et al. 2013; Hsu et al. 2016).

The Acute Kidney Injury – Epidemiologic Prospective Investigation (AKI-EPI), an international cross-sectional study that comprised of 1802 critically ill patients, demonstrated that nephrotoxic drugs were reported as the cause of AKI in 14.4% of patients (Awdishu 2017; Hoste et al. 2015). The AKI–EPI study, jointly with other observational studies, showed that the frequency of DIN is approximately 14–28% in critically ill adult patients (Awdishu 2017; Hoste et al. 2015; Uchino et al. 2005; Acute Renal Failure Trial Network et al. 2008). Critically ill patients receive twice the number of drugs when compared to non–critically ill patients, thus increasing their risk of developing significantly more adverse drug events, including events such as AKI. Nearly 20% of the drugs prescribed in the intensive care unit are considered nephrotoxic. Additionally, drugs are the 3rd to 5th leading cause of AKI in this setting, following sepsis and hypotension (Perazella 2018; Kane-Gill and Goldstein 2015; Awdishu 2017; Bentley et al. 2010).

The epidemiology of drug-induced tubular disorders is unclear, as there is a lack of a standard definition for the disorder. Many published cases have reported that tubular dysfunction leads to AKI. This may underestimate the true incidence of tubular disorders, as only cases associated with changes in serum creatinine (Scr) are recognised. Knowledge of glomerular injury is also unclear, as it is rare, and the publications made are limited to case reports and case series (Awdishu and Mehta 2017).

6.3 Factors Related to Drug-Induced Nephrotoxicity

The plan of the clinical pharmacist to create interventions aimed at avoiding DIN and for optimising drug therapy should evaluate the risk of nephrotoxicity due to the drugs prescribed, (Coulter 2018) and the over-the-counter medications (OTC) used by patients. The development of DIN can be interpreted by examining the factors that determine nephrotoxicity. Additionally, the exposure to a probable nephrotoxic drug, acts as an essential requirement to the interpretation. The chemical structure of the drug, its dose, drug metabolism, excretory mechanism through the kidney, among other characteristics, contribute to the risk of DIN. Comorbid conditions, the

genetic determinants of drug metabolism, transport proteins, and drug transporters, are underlying patient characteristics that are also important in drug nephrotoxicity. As the kidney metabolises and excretes (through filtration and tubular secretion) many administered drugs, the interaction of these substances with various parts of the nephron may be associated with nephrotoxicity (Perazella 2018; Kane-Gill and Goldstein 2015; Awdishu and Mehta 2017).

Drugs observed to result in nephrotoxicity, exert their kidney injury via one or more mechanisms. Generally, for the occurrence of kidney injury, a combination of risk factors related to patient, kidney and drug should be present (Perazella 2018; Awdishu and Mehta 2017).

6.3.1 Risk Factors Related to Drug

Drug characteristics and various mechanisms of drug action play a role in the development of kidney injury. Consequently, the first step in this development involves exposure to a potentially nephrotoxic agent (Perazella 2018). During ambulatory care and hospitalisation, patients are exposed to a variety of potential nephrotoxic substances such as prescribed therapeutic medications, diagnostic agents, over-the-counter products, herbal drugs, and environmental agents, which are presented in Table 6.1.

Exposure to a nephrotoxic medication is one the most significant modifiable risk factor in kidney injury. In clinical practice, examples of known potentially nephrotoxic drugs include antimicrobial agents, immunosuppressive agents, and antineoplastic drugs (Perazella 2018; Awdishu 2017; Bentley et al. 2010; Mehta et al. 2015; Awdishu and Mehta 2017). Presently, targeted therapies and novel immunotherapies serve as effective cancer therapies; however, they have contributed to the increase in occurrence of drug-induced acute and chronic kidney injury in cancer patients. Moreover, a greater number of new medications with unknown nephrotoxic potential have passed through clinical trials, and subsequently released into clinical practice where these drugs cause kidney injury (Schissler et al. 2013; Hsu et al. 2016; Rosner and Perazella 2017; Izzedine and Perazella 2017a). This occurrence is likely related to the exposure of these new drugs to patients who have comorbidities or other characteristics that increase their nephrotoxic risk, which were not included in the clinical trials (Perazella 2018; Rosner and Perazella 2017; Izzedine and Perazella 2017a).

In evaluating the risk of nephrotoxicity caused by drug use, it is important to identify the known risk, the predictable risk (based on the pharmacology of the drug), the chemical characteristics of the drug that contribute to its risk, as well as other contributing risk factors, and the typical timeline of injury. The information available to assess the known risks of DIN is frequently obtained from case reports, or adverse events reported from clinical trials, or through post-marketing surveillance. Prospective studies focused on determining the incidence of DIN are scarce (Perazella 2018; Kane-Gill and Goldstein 2015; Awdishu 2017; Bentley et al. 2010; Mehta et al. 2015; Awdishu and Mehta 2017).

Table 6.1 Nephrotoxins that induce kidney disease

Therapeutic class	Nephrotoxin (Perazella 2018; Bentley et al. 2010; Mehta et al. 2015; Awdishu and Mehta 2017; Shepshelovich et al. 2017; Daudon et al. 2018; Hall et al. 2014; Haque et al. 2012; Paueksakon and Fogo 2017; Markowitz et al. 2015; Rosner and Perazella 2017; Izzedine and Perazella 2017a; Perazella and Shirali 2018; Izzedine and Perazella 2017b)
Antimicrobial drugs	
Aminoglycosides	Amikacin, Gentamicin, Tobramicin
Antiviral	Aciclovir, Abacavir, Atazanavir, Adefovir, Didanosine, Cidofovir, Foscarnet, Indinavir, Lamivudine, Ritonavir, Valaciclovir, Telaprevir, Tenofovir
Beta-Lactam Antibacterials	Amoxicilin, Ampicillin, Cefazolin, Ceftazidime, Oxacillin, Piperacillin- Tazobactan,
Polyenic antifungal antibiotics	Amphotericin B
Polymixins	Colistin, Polymixin B
Sulphonamides	Sulphadiazine, Sulphamethoxazole-Trimetroprim
Quinolones	Ciprofloxacin, Levofloxacin
Glycopeptides	Vancomicin
Others antimicrobial drugs	Rifampin, Tetracicline
Antineoplasic drugs	
Nitrogen mustard analogues	Ifosfamide
Cytotoxic antibiotics	Mitomycin
Platinum compounds	Cisplatin, Carboplatin∗, Oxaliplatin∗ ∗ Less nephrotoxic than cisplatin
Pyrimidine analogues	Gencitabine, Fluorouracil
Folic acid analogues	Methotrexate, Pemetrexede
Anti-vascular endothelial growth factor	Bevacizumab
Tyrosine Kinase inhibitors	Axatinib, Crizotinib, Dabrafenib, Imatinib, Sunitinib, Sorafenib, Pazopanib, Vermurafenib
Immune checkpoint inhibitors	Ipilimumab, Nivolumab, Pembrolizumab
Epidermal growth factor receptor inhibitors	Cetuximab, Panitumumab, Gefitinib, Erlotinib
Immunotherapeutic agents	Interleukin-2 (high dose), Interferons
Other antineoplastic agents	Aflibercept, Abatacept, Bortezonibe, Bleomycine, Daunorrubicin, Lenalidomide, Pentostatin
Bisphosphonates	Pamidronate, Zoledronic Acid
Analgesic	Acetilsalicyic acid, Nonsteroidal anti-inflammatory drugs, Selective cyclo-oxygenase-2 inhibitors
Immunosuppressives	
Calicineurin inhibitors	Cyclosporine, Tacrolimus
Selective immunosuppressants	Everolimus, Sirolimus, Mycophenolate mofetil

(continued)

Table 6.1 (continued)

Therapeutic class	Nephrotoxin (Perazella 2018; Bentley et al. 2010; Mehta et al. 2015; Awdishu and Mehta 2017; Shepshelovich et al. 2017; Daudon et al. 2018; Hall et al. 2014; Haque et al. 2012; Paueksakon and Fogo 2017; Markowitz et al. 2015; Rosner and Perazella 2017; Izzedine and Perazella 2017a; Perazella and Shirali 2018; Izzedine and Perazella 2017b)
Cardiovascular drugs	
Agents Acting on The Renin-Angiotensin System	Angiotensin-receptor blockers, Angiotensin-converting enzyme inhibitors, Renin inhibitors
Diuretics	Bumetamide, Furosemide, Spironolactone
Lipid Modifying Agents	Statins
Others cardiovascular drugs	Amlodipine, Digoxin, Hidralazine
Blood substitutes and plasma protein fractions	Dextran, Hydroxyethyl starch, Mannitol,
Platelet aggregation inhibitors	Clopidogrel, Prasugrel, Ticlodipine,
Drugs for peptic ulcer and gastro-oesophageal reflux disease	Cimetidine, Omeprazole, Lansoprazole, Ranitidine
Others	Acetazolamide, Anabolic steroids, Alendronate, Allopurinol, Anti-thymocite globulin, Edelcalcitol, Edravone, Intravenous immunoglobulin, Lithium carbonate, Infliximab, Mesalazine, Methimazole, Metformin, Muromonab (OKT3), Orlistat, Propylthiouracil, Sucrose, Topiramate, Zonisamide
Diagnostic agents	Gadolinium (in high dose), Oral sodium phosphate (colonoscopy preparation), Radiocontrast media
Illicit drugs	Cocaine, Heroin
Herbal medicines	*Aristolochic acid, Ephedra sp, Glycyrrhiza sp., Datura sp., Taxus celebica, Uno degatta, Cape aloes*

6.3.1.1 Drug Characteristics

Regarding the drug characteristics, it is important to consider the solubility, chemical structure and charge of the drug. Drugs and metabolites that are insoluble in the urine may result in acute crystalline nephropathy by precipitating in the distal tubular lumens. This process is further enhanced by reduced urinary flow rates, urine pH (depending on the pKa), excessive drug dosing, and rapid infusion rates. Besides obstructing urinary flow, precipitated crystals induce inflammation in the surrounding interstitium. Drugs that induce the development of crystalline nephropathy include methotrexate, acyclovir, indinavir, atazanavir, sulphadiazine, ascorbic acid, oral sodium-phosphate, and triamterene (Perazella 2018; Shepshelovich et al. 2017).

Positive charge is a drug characteristic that enhances nephrotoxicity. The charge of polycationic aminoglycosides is positive, therefore they are attracted to the negatively-charged proximal tubular membrane phospholipids. The aminoglycoside nephrotoxicity is in part associated with their cationic charge. Neomycin has a

higher cationic charge and is more nephrotoxic than amikacin, which has a lower cationic charge (Perazella 2018; Rougier et al. 2003; Nagai and Takano 2004).

Dextran, hydroxyethyl starch, and sucrose with immunoglobulin, are drugs associated with osmotic nephropathy that accumulate within the phagolysosomes of proximal tubular cells. Due to their structure, these drugs cannot be metabolised, and ultimately result in lysosomal dysfunction and cell swelling (Perazella 2018; Orbach et al. 2004; Dickenmann et al. 2008).

6.3.1.2 Dosing of Drugs

High doses and prolonged courses of exposure to specific nephrotoxins, will enhance the risk of kidney injury due to excessive exposure. This will even occur in patients with minimal or no underlying risk of such injury. This category includes the following drugs: aminoglycosides, cisplatin, amphotericin B and colistin (Perazella 2018; Awdishu and Mehta 2017; Blatt and Liebman 2013; Perazella and Rosner 2018).

Assessing kidney function is critical in the dosing of drugs and in mitigating DIN (Perazella 2018; Eppenga et al. 2016). Dosage adjustment based on excretory renal function is required for many medications. However, there is a lack of consensus for the best strategy to estimate glomerular filtration rate or the excretory function, for the aim of drug therapy (Eppenga et al. 2016; Delanaye et al. 2017; Hudson and Nolin 2018). The following equations are available for use in clinical practice: Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and Cockcroft-Gault. These formulas are all based on Scr levels (Awdishu and Mehta 2017; Eppenga et al. 2016; Delanaye et al. 2017; Hudson and Nolin 2018); however, there are several factors (muscle mass, liver function, age, muscular dystrophy, spina bifida, to name a few) that may influence SCr, and may provide an estimate for the glomerular filtration rate, without demonstrating the true glomerular filtration rate itself (Awdishu and Mehta 2017; Eppenga et al. 2016). Inaccuracy in the estimated glomerular filtration rate values may lead to a subsequent inaccuracy in the estimation of kidney function, with an overestimation contributing to the administration of larger doses than required. This may then result in supratherapeutic dosing and adverse drug events. Conversely, an underestimation may lead to subtherapeutic dosing, therefore resulting in treatment failure and prolonged illness (Eppenga et al. 2016; Hudson and Nolin 2018). Clinical pharmacist and other health practitioners must be vigilant in the assessment of kidney function in order to provide optimal drug therapy (Eppenga et al. 2016; Delanaye et al. 2017; Hudson and Nolin 2018). The determination the most appropriate dosing regimen SCr-based formulas should never be used naively but always in combination with clinical and pharmacotherapy assessment of the individual patient (Eppenga et al. 2016).

6.3.1.3 Drug Interactions

The drug class combinations or drug interactions increase kidney injury and the overall drug toxicity (Perazella 2018; Rivosecchi et al. 2016). This especially occurs during hospitalisation where patients may receive multiple nephrotoxic agents, resulting in additive or synergic adverse renal effects (Rivosecchi et al. 2016). The pathway of excretion via the kidney, represents another risk for drug nephrotoxicity. Drugs compete with substances (and others drugs) produced endogenously, for transport proteins and influx/efflux transporters, which can increase intracellular drug concentration and the risk of kidney injury. Therefore, pharmacokinetic drug-drug interactions increase kidney injury and overall drug toxicity (Perazella 2018).

Limited data are available for the true incidence and severity of harm, that result from the drug combinations associated with AKI. A review of the literature performed by Rivossechi et al. showed that the combinations with the best evidence of increased risk of AKI are NSAIDs-diuretics, NSAIDs-RAAS (Renin-Angiotensin System) agents, statin-macrolide, and macrolide-calcium channel blocker. Information regarding the mechanism of AKI for drug class combinations is however scarce. This lack of definitive mechanisms, makes it difficult for providers to determine if the drug combinations result in a synergistic or additive AKI potential, that may ultimately alter prescribing practices (Rivosecchi et al. 2016) Table 6.2 includes the information for the common drug class combinations prescribed in a clinical practice, as is identified in the review of the literature performed by Rivossechi et al. (2016).

Vancomycin plus piperacillin-tazobactam is one of the most commonly used combinations of antimicrobials, with widespread use in hospitals (Rivosecchi et al. 2016; Luther et al. 2018). A systematic review and meta-analysis showed that the combination of vancomycin and piperacillin-tazobactam increases the odds of AKI three-fold. This increased risk was identified when compared to vancomycin monotherapy, vancomycin plus cefepime or carbapenem, and piperacillin-tazobactam monotherapy. Although there was limited data, the analysis of critically ill patients suggests the odds of AKI with vancomycin plus piperacillin-tazobactam increase over vancomycin monotherapy, while being mitigated when compared to vancomycin plus cefepime or carbapenem (Luther et al. 2018).

6.3.1.4 Intrinsic Drug Nephrotoxicity

Aminoglycosides, amphotericin B, the polymyxins and cisplatin are examples of drugs that maintain higher potentials for causing kidney injury, as they exhibit more significant intrinsic nephrotoxicity. These drugs may cause kidney injury at the therapeutics doses and brief durations of exposure (Perazella 2018; Awdishu 2017; Bentley et al. 2010).

The intrinsic nephrotoxicity of aminoglycosides is related to their positive charge. Accumulation of high concentrations of the polycationic aminoglycosides within intracellular lysosomes causes lysosomal injury, which is associated with

Table 6.2 Grade level of evidence for some of the drug class combinations related to acute kidney injury

Combination		Grade level of evidence	Mechanism of Nephrotoxicity
Drug 1	Drug 2		
Calcium channel blockers	Clarithromycin	Moderate	Renal injury through CYP3A4 inhibition of clarithromycin, leading to elevated concentrations of calcium channel blockers (both dihydropyridine and nondihydropyridine) (Rivosecchi et al. 2016; Gandhi et al. 2013)
Eplerenone	Loop diuretic	Moderate	Unknown (Rivosecchi et al. 2016; Rossignol et al. 2012)
Gentamicin	Polygeline 3.5%	Moderate	High calcium content of polygeline (6.25 mmol/L) would potentiate the nephrotoxic effects of aminoglycosides (Rivosecchi et al. 2016; Schneider et al. 1996)
NSAID	Diuretic	Moderate	Pharmacodynamic effect on the kidney, with a decrease in prostaglandin synthesis by NSAIDs causing afferent vasoconstriction, and a decrease in effective blood volume caused by diuretics (Rivosecchi et al. 2016; Steinhäuslin et al. 1993)
NSAID	Diuretic and RAAS	Moderate	NSAIDs decrease prostaglandin synthesis, creating afferent arteriolar vasoconstriction, which is exacerbated by the efferent arteriolar vasodilation caused by the RAAS agents. Lastly, diuretics decrease renal blood flow through the reduction of plasma volume, leading to decreased renal perfusion pressure (Rivosecchi et al. 2016; Lapi et al. 2013)
Piperacillin/ Tazobactam	Vancomycin	Moderate	Decreased vancomycin clearance caused by piperacillin/tazobactam potentially leading to a greater degree of vancomycin exposure (Rivosecchi et al. 2016; Luther et al. 2018; Burgess and Drew 2014)
Statins	Macrolides	Moderate	Increased serum statin concentrations as a result of inhibition of the cytochrome 450 (CYP450) enzyme system by macrolide. This increase in serum statin concentrations leads to an increased risk of rhabdomyolysis (Rivosecchi et al. 2016; Patel et al. 2013)
Statins	Calcium Channel blockers	Moderate	Increased exposure to statin and an increased risk of development of rhabdomyolysis (Rivosecchi et al. 2016; Wang et al. 2016)
Cisplatin	Aminoglycoside	Low	Both drugs are nephrotoxic (Rivosecchi et al. 2016; Christensen et al. 1989)
Gentamicin	Cephalosporin	Low	There has not been a clearly elucidated mechanism for renal injury (Rivosecchi et al. 2016; Cabanillas et al. 1975; Fillastre et al. 1973)

(continued)

Table 6.2 (continued)

Combination		Grade level of evidence	Mechanism of Nephrotoxicity
Drug 1	Drug 2		
Cyclosporine	Ciprofloxacin	Very low	Ciprofloxacin decreases the metabolism of cyclosporine, thus elevating cyclosporine concentration (Rivosecchi et al. 2016; Elston and Taylor 1988; Nasir et al. 1991)
Diuretic	RAAS agents	Very low	Diuretics inhibit the tubulo-glomerular feedback systems along with activation of RAAS (Rivosecchi et al. 2016; Wrenger et al. 2003; Lee and Pettinger 1992)
Methotrexate	NSAIDs	Very low	Elevated methotrexate concentrations caused by a decrease in renal perfusion, secondary to the inhibition of prostaglandin synthesis by NSAIDS (Rivosecchi et al. 2016; Maiche 1986; Singh et al. 1986)
Simvastatin	Cyclosporine	Very low	Pharmacokinetic drug-drug interaction caused by cyclosporine decreases the embolism of statins through CYP450 inhibition (Rivosecchi et al. 2016; Teutonico et al. 2010; Scarfia et al. 2013; Kusus et al. 2000; Hamill 2013)
Statins	Fenofibrates	Very low	Nephrotoxicity results from the development of rhabdomyolysis. It is unclear if this is a result of an interaction at the skeletal muscle or through a CYP450 –mediated drug interaction (Rivosecchi et al. 2016)

phospholipid membrane injury, oxidative stress, and mitochondrial dysfunction. This promotes proximal tubular cell apoptosis and necrosis with clinical manifestations such as an isolated proximal tubulopathy or AKI (Perazella 2018; Rougier et al. 2003; Nagai and Takano 2004).

Nephrotoxicity is a factor that limits the use of amphotericin B, which is associated with substantial morbidity, mortality, and elevated healthcare costs. The high prevalence of nephrotoxicity resulting from the use of amphotericin B deoxycholate, is induced by kidney injury. This injury is caused by a disruption in tubular cell membranes and an increase in permeability to cations, subsequently leading to tubular dysfunction due to cell swelling/dysfunction. Less nephrotoxicity is ascribed to lipid/liposomal formulations (Perazella 2018; Zavascki and Nation 2017).

Colistin and Polymyxin B are highly nephrotoxic with very narrow therapeutic indexes. The nephrotoxicity of these antimicrobial agents is related to their D-amino acid content and fatty acid component, which results in an increase in cellular membrane permeability and allows cation influx. This effect subsequently leads to tubular cell swelling and lysis, with AKI development (Perazella 2018; Guo and Nzerue 2002).

Tenofovir, an acyclic nucleotide phosphonate widely used to treat hepatitis B virus and HIV infection, enters the cell via the basolateral human organic anion

transporter −1 (hOAT-1). In addition, tenofovir induces cellular injury primarily through disturbing the mitochondrial function associated with proximal tubulopathy and AKI (Perazella 2018).

Antiangiogenesis therapy with monoclonal antibodies against vascular endothelial growth factor (VEGF), circulating soluble VEGF receptors, and small molecule tyrosine kinase inhibitors that impair the intracellular VEGF signalling pathways, are associated with various types of kidney injury. A reduction in VEGF levels or signalling pathways by antiangiogenic drugs, promotes loss of healthy fenestrated endothelial phenotype; which is important in the normal functioning of the glomerular basement membrane. This loss induces microvascular injury and thrombotic microangiopathy, resulting in proteinuria and AKI (Perazella 2018; Mehta et al. 2015; Haque et al. 2012).

6.3.2 Risk Factors Related to Patient

Being of an older age and the female gender are non-modifiable risk factors of nephrotoxicity. These factors are associated with a decrease in lean body mass and a reduction in total body water, that can lead to excess drug dosing (Perazella 2018; Awdishu and Mehta 2017). Women and the elderly have hypoalbuminemia which results in reduced drug binding and increased free drug concentrations that can be nephrotoxic (Perazella 2018; Khan et al. 2017; Hamill 2013). The elderly also have an increased propensity to vasoconstriction from excessive circulating angiotensin II and endothelin levels, and have a higher level of biomarkers modified via oxidation. These factors combine to increase patient exposure to excess drug concentrations and their nephrotoxicity risk (Khan et al. 2017; Jerkić et al. 2001).

Chronic kidney disease, AKI, nephrotic syndrome, liver diseases (advanced cirrhosis, obstructive jaundice), cancer, and diabetes are important risk factors in DIN (Perazella 2018). Multiple myeloma, lymphoma and leukaemia, renal cell cancer and other neoplasms are often associated with enhanced DIN. Besides, these comorbid conditions, sepsis and metabolic disturbances increase the risk of adverse kidney effects with certain drugs. Sepsis due to its associated systemic and renal hemodynamic alterations, as well as the synergistic effect between endotoxin and nephrotoxic drugs, increases the risk of DIN (Izzedine and Perazella 2017a).

The risk of nephrotoxicity also increases in patients with effective volume congestive that is associated with heart failure, and a true depletion volume from vomiting, diarrhoea and diuretics (Perazella 2018; Izzedine and Perazella 2017a).

Altered kidney perfusion from reduced effective circulating blood volume, and hypoalbuminemia with free circulating drug levels, are mechanisms that explain the nephrotic syndrome, with cirrhosis enhancing nephrotoxic risk. Another liver disease, obstructive jaundice, also enhances the toxicity to certain drugs including aminoglycosides, by altering the haemodynamics such as decreased renal flow and direct the toxic effects of bile salts in the tubular epithelia (Perazella 2018; Fanos and Cataldi 2001).

Hypokalaemia, hypomagnesemia, and hypocalcaemia are electrolyte disorders that increase the nephrotoxicity associated with aminoglycosides. Hypomagnesemia may also exacerbate cisplatin toxicity. Severe hypercalcaemia leads to afferent arteriolar vasoconstriction, tubular sodium and water wasting, thus inducing prerenal physiology which increases nephrotoxic drug injury (Perazella 2018).

Systemic metabolic acidosis or alkalosis may decrease or increase urine pH, whereas proximal and distal renal tubular acidoses are associated with alkaline urine as they impair the kidney's ability to excrete H^+ ion. Acidic urinary pH (<5.5) increases intratubular crystal deposition with drugs such as sulphadizine, methotrexate, and triamterene, as they have limited solubility in a low-pH environment. A urine pH >6.0 increases crystal precipitation within the tubular lumens by drugs such as indinavir, atazanavir, oral sodium phosphate solution, and ciprofloxacin. Drugs that are carbonic anhydrase inhibitors such as topiramate, zonisamide and acetazolamide, induce the formation of alkaline urine, thereby promoting the precipitation of calcium-phosphate within tubules, and enhancing the risk of developing nephrolithiasis (Perazella 2018; Daudon et al. 2018).

Pharmacogenetics should also be considered as a factor that assists in the understanding of the vulnerability of patients to potential nephrotoxins. Studies have suggested that the metabolic pathways, transport proteins, and drug transporters vary between patient populations due to the effect of genetic composition. The hepatic cytochrome P450 enzyme system has gene polymorphisms that are associated with reduced drug metabolism, and subsequently leads to end organ toxicity. Considering that the kidney also possesses CYP450 enzymes that participate in drug metabolism, it is expected that gene polymorphisms favouring reduced drug metabolism could increase the nephrotoxic risk (Perazella 2018; Suk et al. 2005).

Polymorphisms of genes encoding proteins are involved in the metabolism and the subsequent elimination of drugs by the kidneys, and the repair pathways after injury also correlate with various levels of drug sensitivity. The increased risk of nephrotoxicity with an exposure to cisplatin can be explained by the polymorphisms in cytosolic glutathione-S-transferase enzymes, which normally function to detoxify reactive molecules such as cisplatin (Suk et al. 2005; Izzedine et al. 2006).

6.3.3 Risk Factors Related to Kidney

A high renal blood flow increases drug delivery and exposes the kidney to a significant amount of drug concentration. Moreover, the excessive cellular workload of the loop of Henle and many tubular cells in one relatively hypoxic environment, also enhance the risk of a nephrotoxic-related injury. Kidney injury can be induced through direct toxicity as well as ischemic damage from reduced prostaglandin and increased thromboxane production. This injury is a consequence of the increased drug concentrations within the kidney medulla and interstitium (Perazella 2018).

Besides hepatic metabolism, a great number of drugs undergo biotransformation by the kidney enzyme systems, including CYP450 and the flavin-containing mono-

oxygenases. The metabolism of drugs to toxic metabolites and reactive oxygen species by the kidney, overwhelms the local antioxidants and promotes tubular injury as observed with aminoglycosides, cisplatin, and several other medications (Perazella 2018; Fanos and Cataldi 2001; Izzedine et al. 2006).

Another important avenue of kidney injury occurs with the excretion of drugs via the active transporters in the proximal tubular cells. Extensive tubular cell uptake of potential nephrotoxic drugs via both the apical and basolateral transport systems, underlies the development of kidney injury. Apical drug uptake via endocytosis or pinocytosis leads to drug accumulation. This triggers an injury cascade leading to cell injury and death, which are presented clinically as proximal tubulopathy and/or AKI. Basolateral drug transport via the human organic anion transporters (hOAT) and human organic cation transporters (hOCT) also lead to drug accumulation (Perazella 2018).

In summary, common risk factors of DIN include age, causal drug, single and/or cumulative dosing, the underlying CKD, comorbid diseases and concurrent nephrotoxin exposures. Minimising the exposure to risk factors may mitigate the development of DIN.

6.4 Recognition of Drug-Induced Nephrotoxicity

The recognition of DIN by clinical pharmacist is important when planning the course of care for the patient, and in avoiding future harm to the patient (Coulter 2018; Kane-Gill and Bauer 2017). This recognition should be made based on a defined Scr criteria, the clinical phenotype, concurrent risk factors, and the causality assessment (Awdishu 2017; Mehta et al. 2015; Awdishu and Mehta 2017). The KDIGO Scr criterion is available for use in clinical practice (Kidney Disease 2012; Chawla et al. 2017).

Presently, a standard definition for DIN does not exist, and the incidence of nephrotoxicity varies depending on the definition employed and the causal drug. The definition that is most described in studies considers nephrotoxicity as 0.5 mg/dl or a 50% rise in the Scr level over a 24–72 h period, and a minimum 24–48 h of drug exposure. These definitions however result in challenges, since a 50% increase in Scr may not have high specificity for DIN as the underlying disease being treated, and other AKI risk factors could be significant in the attribution of the risk. In the setting of a fluctuating renal function, or in patients receiving replacement therapies, it is also difficult to recognise DIN (Mehta et al. 2015; Awdishu and Mehta 2017).

DIN was categorised by Mehta et al. into three broad subsets reflecting the time course of the events. These categories were built on conceptual models proposed by KDIGO (Kidney Disease 2012; Chawla et al. 2017) for AKI (which considers if the injury develops within 7 days or less), acute kidney diseases (injury lasts beyond 7 days but less than 90 days) and CKD (persistence of injury for >90 days). The development of DIN can similarly be divided into acute (1–7 days), sub-acute

(8–90 days) and chronic (>90 days) DIN after drug exposure. This approach permits the classification and tracking of injuries for their duration and outcomes (Mehta et al. 2015).

The Scr used for defining DIN should be as close as possible to the event, to meet the definition of AKI. However, it is important to highlight that in the case of ambulatory cases, exposures may not always be available. In the setting of outpatient care, it is recommended that the lowest Scr within 90 days of the event, be used as the reference Scr. The CKD is described as an important risk factor for the development of DIN. The underlying kidney disease impacts the recognition of DIN. To define the CKD, it is recommended that the Scr value greater than 90 days from the DIN event, be used (Mehta et al. 2015; Awdishu and Mehta 2017).

To improve the recognition of DIN, it is important to know the clinical presentation of the phenotypes of DIN, and their causal criteria (Mehta et al. 2015; Awdishu and Mehta 2017).

6.5 Phenotypes for Drug-Induced Nephrotoxicity

The phenotypes for DIN was established by the modified Delphi process which considers the known mechanism of nephrotoxicity, time course of drug exposure and the setting. The panel was composed of international, adults and paediatric nephrologists and pharmacists. The development of standardised phenotypes for DIN was supported by the International Serious Adverse Event Consortium (Mehta et al. 2015).

The panel proposed four phenotypes for DIN, based on the clinical presentation: AKI, tubular disorders, glomerular injury, and nephrolithiasis. To standardise the initial phenotype, the panel developed primary and secondary criteria. At least one primary criterion must be met for all drugs suspected of causing DIN. For each phenotype definition, the following critical elements from the Bradford-Hill causal criteria must be met: (i). The drug exposure must be at least 24 h preceding the event; (ii). There should be a biological plausibility for the causal drug, based on the known mechanism of the drug effect; metabolism and immunogenicity; (iii). Complete data (including, but not limited to, co-morbidities, medication history, additional nephrotoxic exposures, exposure to contrast agents, surgical procedures, blood pressure, urine output, biomarker concentrations, concurrent risk factors) surrounding the period of drug exposure is required to account for concomitant risks, and exposures to other nephrotoxic agents; iv. The strength of the relationship between the suspected drug and phenotype should be based on drug exposure duration, extent of which the primary and second criteria are met, and the time course of the injury (Awdishu 2017; Awdishu and Mehta 2017).

The primary and second criteria for each of the four phenotypes for DIN are detailed in the International Serious Adverse Event Consortium report that provides the phenotype standardisation for DIN (Mehta et al. 2015).

6.5.1 Acute Kidney Injury

The AKI phenotype was based on the KDIGO Criteria, with modifications to account for the presence of underlying CKD, time course, and setting (Mehta et al. 2015; Kidney Disease 2012; Chawla et al. 2017). The clinical characteristics of AKI encompass acute tubular necrosis, acute interstitial nephritis and osmotic nephrosis.

The changes in Scr are important parameters to the AKI phenotype. Although haemodynamic changes are recognised using drugs such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and nonsteroidal anti-inflammatory drugs (NSAIDs), there are currently no consensus definitions for haemodynamic injury. As transient changes in creatinine (usually stage 1 AKI) can occur due to other factors (for example, the dehydration and hypotension in the setting of drug exposure), and resolve when these factors are corrected, it is often difficult to distinguish the primary drug-induced effects, from others factors. The Translational Research Investigating Biomarker Endpoints in AKI (TRIBE-AKI), a multicentre study, suggested that in cardiac surgery patients exposed to angiotensin-converting enzyme inhibitors, the changes by the angiotensin receptor blockers are generally mild (stage 1 criteria). However, this may be resolved with a dose reduction or withdrawal, and may not represent a clinically significant injury (Mehta et al. 2015; Koyner et al. 2014). To increase the specificity for standardisation, the panel for the consensus did not include haemodynamic changes as a distinct criterion, and they proposed that the primary criteria must meet a minimum of the KDIGO stage 2, to be considered as a potential DIN event. Thus, the overall severity of AKI should be based on the KDIGO staging criteria (Mehta et al. 2015; Kidney Disease 2012; Chawla et al. 2017).

There are various mechanisms for the AKI phenotype. For example, renal functional change can reflect a direct nephrotoxic effect (i.e. acute tubular necrosis from aminoglycoside or cisplatin), or an idiosyncratic effect (i.e. acute interstitial nephritis from a proton pump inhibitor). In these two circumstances, alterations in Scr and urine output defines the phenotype. Biomarkers of kidney damage combined with functional markers (e.g. Scr and urine output) may permit further delineation of tubulo-interstitial injury including transient haemodynamic alterations and could aid in defining the AKI phenotype (Mehta et al. 2015; Awdishu and Mehta 2017).

6.5.1.1 Renal Biomarkers

Emerging biomarkers of kidney damage [e.g. neutrophil gelatinase–associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), liver-type fatty acid binding protein (L-FABP), N-acetyl-β-D-glucosaminidase-NAG, and tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7 ([TIMP-2]·[IGFBP7])] has been investigated (Mehta et al. 2015; Awdishu and Mehta 2017; Barreto et al. 2018; Redahan and Murray 2018).

Renal biomarkers of damage include proteins whose synthesis is upregulated in AKI, molecules that are released from injured kidney cells, and by-products whose elimination is altered during kidney damage. The release of damage markers into the serum of urine, provides an early signal of AKI in high-risk patients, before a rise in SCr occurs. Having an early indication of kidney damage is important in identifying patients that are most likely to benefit from the discontinuation of nephrotoxic drugs, and also patients in need of closer monitoring and/or preventative and therapeutic interventions (Barreto et al. 2018).

The biomarker NGAL is qualified for use in clinical practice in some countries, and has been shown to identify DIN up to 4–5 days before a rise in SCr occurs (Redahan and Murray 2018). The [TIMP-2]· [IGFBP7] is commercially available in the United States and has been proposed as a method to risk-stratify patients to nephrotoxic medications or conditions, for their potential in developing AKI in the future (Barreto et al. 2018).

Considering the use of novel renal biomarkers, pharmacists should perform the following activities: (i). interpret and apply biomarker test results; (ii). modify therapy using renal dosing protocols; and (iii). develop collaborative practice models to facilitate renal biomarker utilisation (Barreto et al. 2018).

6.5.1.2 Drug-Induced Acute Kidney Injury

A variety of drugs can induce AKI, and some examples are provided in Table 6.3. Identification of new medications associated with AKI requires diligent pharmacovigilance actions (Hosohata et al. 2019; Welch et al. 2018). Nowadays, it is an increasing consensus that a detailed evaluation of the information arising from pharmacovigilance activities is important in ensuring the safe use of all drugs. The safety profile of drugs can change over time as their use expands to patients with different characteristics (Hosohata et al. 2019). Some countries have an adverse drug reactions database, combining the information from manufacturers, with voluntary reports submitted by health care providers. These databases are a powerful tool to analyse the association between drugs and adverse drug events. Using these database, it is possible to calculate the reporting odds ratio (ROR) (Hosohata et al. 2019; Welch et al. 2018). The ROR is a measure of the relative risk of drug-associated adverse event, and corresponds to the risk of spontaneous notification of an adverse drug reaction, and not the risk of adverse drug reaction occurrence per se.(Hosohata et al. 2019) In Japan and the United States, the pharmacovigilance databases were investigated with the aim to identify and classify medications most commonly associated with AKI, and to determine the ROR (Hosohata et al. 2019; Welch et al. 2018). The ROR of tubule interstitial nephritis was investigated in the pharmacovigilance database of Japan (Oyama et al. 2018). These investigations gave data on drugs in need of further research, to determine the risk of drugs, that have not been recognised as nephrotoxic (Hosohata et al. 2019; Welch et al. 2018; Oyama et al. 2018). The drugs with a statistical ROR for AKI and tubulo-interstitial nephritis are shown in Table 6.3.

Table 6.3 Drug -induced acute kidney injury

Renal histopathological features			
Acute Tubular Necrose (Paueksakon and Fogo 2017; Rosner and Perazella 2017; Izzedine and Perazella 2017a; Blatt and Liebman 2013)	Acute Interstitial Nephritis (Acute Renal Failure Trial Network et al. 2008; Paueksakon and Fogo 2017; Perazella and Shirali 2018; Blatt and Liebman 2013)	Drugs with a statistically significant Reporting odds ratio (ROR) of AKI (Redahan and Murray 2018; Hosohata et al. 2019)	Drugs with a statistically significant ROR of tubulo-interstitial nephritis (Welch et al. 2018)
Adefovir, Amikacin, Amphotericin B, Cephalosporin, Cidofovir, Cisplatin, Cyclosporine, Foscarnet, Gentamicin, Ifosfamide, Naproxen, Pemetrexede, Radiocontrast media, Tacrolimus, Tetracicicline, Tobramicin,	5 Aminosallicylates, Aciclovir, Allopurinol, Amoxicilin, Ampicillin, Cefazolin, Ceftazidime, Cimetidine, Colistin, Crizotinib, CTLA-4 inhibitors, Dabrafenib, Indinavir, Ipilimumab, Lanzoprazole, Nafcillin, Nivolumab, Nonsteroidal anti-inflammatory drugs, Omeprazole, Oxacillin, Pazopanib, PD-1inhibitors, Pembrolizumab, Piperacillin- Tazobactan, Proton Pump Inhibitors, Ranitidina, Rifampin, Selective cyclo-oxygenase-2 inhibitors, Sorafenib, Sunitinib, Vancomicin, Vermurafenib	Acetylsalicylic acid, Aciclovir, Alendronate, Aliskeren Allopurinol, Amlodipine, Anti-thimocyte Globulin, Atorvastatin, Bevacizumab, Bortezonib, Carboplatin, Ceftriaxone, Ciprofloxacin, Cisplatin, Cyclosporine, Dabigatran, Deferasirox, Diclofenac Digoxin, Edelcalcitol, Edravone Emtricitabine -tenofovir, Enalapril, Etarnecept, Everolimus, Everolimus, Fluorouracil, Furosemide, Ibuprofen, Imatinib, Lenalidomide, Levofloxacin, Candersartan, Lisinopril, Lithium Carbonate, Loxoprofen, Metformin, Methotrexate, Mycophenolate mofetil, Mycophenolic acid, Olmersatan, Omeprazole, Oral sodium phosphate (colonoscopy preparation) Pamidronate, Piperacillin-Tazobactan, Ramipril, Rituximab, Rofecoxib, Rosuvastain Simvastatin, Sirolimus Spironolactone, Sulphamethoxazole-Trimetroprim Sunitib, Sunitinib, Tacrolimus, Telaprevir Valaciclovir, Valsartan, Vancomicin, Zoledronic Acid	Abacavir, Acetaminophen, Acetylsalicylic acid, Adefovir, Allopurinol, Amlodipine, Amoxicillin, Ampicillin -sulbactam, Atazanavir Atorvastatin, Benidipine, Candesartan Cilexetil, Carbamazepin, Carbocisteine, Cefazolin, Cefcapene pivodil, Cefdinir, Cefditoren pivoxil, Cefteram pivoxil, Ceftriaxone sodium, Celecoxib, Clarithroycin, Diclofenac, Eldecalcitol, Enalapril, Ethambutol, Famotidine, Garenoxacin, Gliclazide, Glimepiride, Ibuprofen, Isoniazid, Ketoprofen, Lamivudine, Lanzoprazole, Levofloxacin, Limaprost alfadex, Loratadine, Loxoprofen, Mefenamic acid, Meropenem, Mesalazine, Minocycline, Montelukast, Moxifloxacin, Omeprazole, Piperacillin, Piperacillin-tazobactam, Polaprezinc, Pregabalin, Pyrazinamide, Rabamipide, Rabeprazol, Rifampicin, Risedronate, Rosuvastatin, Sodium Valproate, Tenegliptin, Tosufloxacin tosilate, Tretinoin, Trimethoprim-sulphamethoxazole, Ursodeoxycholic acid, Valaciclovir, Vancomycin

6.5.2 Glomerular Disorder

Glomerular injury induced by drug exposure includes direct cellular toxicity or immune mediated injury (Mehta et al. 2015; Paueksakon and Fogo 2017; Markowitz et al. 2015). The specific glomerular cell that is targeted by the nephrotoxins determine the clinical presentatation (Markowitz et al. 2015). The visceral epithelial (podocyte) cell and the endothelial cell are related to drug-induced glomerular diseases (Paueksakon and Fogo 2017). The glomerular lesions associated with direct cellular toxicity include thrombotic microangiopathy, minimal change glomerular disease, and focal segmental glomerulosclerosis. Lesions from immune-mediated injury include vasculitis and membranous nephropathy (Mehta et al. 2015). Although a variety of drugs have been implicated in glomerular injury, this is not a common form of DIN (Mehta et al. 2015; Awdishu and Mehta 2017). The drugs that have the capacity to induce glomerular disorder is shown in Table 6.4.

Table 6.4 Drug-induced glomerular disorder

Renal histopathological features		
Drug induced Thrombotic Microangipathy (Paueksakon and Fogo 2017; Rosner and Perazella 2017; Izzedine and Perazella 2017a; Perazella and Rosner 2018; Perazella and Shirali 2018)	Drug-induced Podocytopathies (Paueksakon and Fogo 2017; Markowitz et al. 2015; Izzedine and Perazella 2017a; Perazella and Shirali 2018)	Drug-induced glomerular disease, immune-mediated injury (Paueksakon and Fogo 2017; Markowitz et al. 2015)
Aflibercept, Albendazole, Anabolic steroids, Axatinib, Bevacizumab, Bleomycine, Cyclosporine, Carboplatin, Cisplatin, Clopidogrel, Cocaine, Cyclooxigenase 2-inhibitors, Cytarabine, Danourrubicin, Defribrotide, Diclofenac, Dipyridamole, Estramustine, Hormones: conjugated oestrogens alone or combined. Contraceptive combination, Hydroxyurea, Interferons, Iodine, Ketorolac, Lithium, Carbonate, Lomustine, Metronidazole, Mitomycin, Muromonab (OKT3), Pamidronate, Pazopanib, Penicillin, Piroxicam, Prasugrel Quinine, Rifampin, Simvastatin, Sorafenib, sulphasoxazole, Sunitinib, Tacrolimus, Tamoxifen, Tetracycline, Valaciclovir,	Anabolic steroids, Aflibercept, Axatinib Bevacizumab, Gemcitabine, Interferons, Lithium Carbonate, Mitomycin, Nonsteroidal anti-inflammatory drugs, Pamidronate, Pazopanib, Prasugrel, Quinine, Sirolimus, Sorafenib, Sunitinib, Ticlodipine, Zoledronic Acid (rarely)	Abatacept, Adalimunab, Carbimazole, Cocaine, Etanercept, Hidralazine, Infliximab, Levamisole, Methimazole, Procainamide, Propylthiouracil, Tacizumab

Significant proteinuria, haematuria and associated urinary sediment abnormalities are the hallmarks of the glomerular phenotype; however, this must be distinguished from a primary (e.g. idiopathic minimal change disease) or secondary (e.g. diabetes) glomerular process.

6.5.3 Tubular Disorders

Tubular disorders are a type of DIN related to drugs that are handled by the tubular transport mechanisms. It is therefore possible that mutations in renal transporters could give rise to tubular toxicity (Mehta et al. 2015).

Drug-induced tubular disorders have several different mechanisms depending on the site of drug handling, drug exposure, and duration of treatment. In most circumstances, these are dose-related, and are usually seen with chronic, continued exposure (Mehta et al. 2015).

This phenotype includes renal tubular acidosis, Fanconi syndrome, the syndrome of inappropriate antidiuretic hormone, diabetes insipidus and phosphate wasting. By recognising the wide spectrum of tubular disorder, the panel proposed classifying this phenotype to include abnormalities in urinary losses of phosphate glucose, magnesium, potassium, and tubular proteins or water handling. These would be associated with secondary changes in serum electrolytes, bicarbonate, and pH (Mehta et al. 2015). The drugs that induce tubular disorders are shown in Table 6.5.

Table 6.5 Drug-induced tubular dysfunction

Proximal renal tubular acidosis (Haque et al. 2012)	Proximal renal tubular acidosis with Fanconi syndrome (Haque et al. 2012)	SIADH[a] (Shepshelovich et al. 2017)
Acetazolamide BrinzolamideDorzolamideTopiramate	Acetylsalicylic acid Adefovir Amikacin Carboplatin Cidofovir Cisplatin Deferasirox Degraded tetracycline Didanosine Gentamicin Ifosfamide Imatinib mesylate Oxaliplatin Sodium Valproate Stavudine Tenofovir	Amitriptyline Carbamazepin Citalopram Cyclophosphamide Duloxetin Escitalopram Haloperidol Mirtazapine Paroxetine Phenytoin Pregabalin Risperidone Sodium Valproate Tramadol Venlafaxine Vincristine

[a]SIADH does not reflect direct tubular damage, but rather the impact of a drug on ADH secretion and subsequent impairment in water handling (Mehta et al. 2015)

6.5.4 Nephrolithiasis

The overall prevalence of drug-induced nephrolithiasis is estimated to be 1–2% of all causes of nephrolithiasis. Drug-induced nephrolithiasis can be a result of abnormal crystal precipitation in the renal collecting system. This may potentially cause pain, haematuria, and infection, or occasionally, urinary tract obstruction with kidney injury. Drugs may precipitate into crystals depending on their urinary solubility. Another group of drugs induced the formation of urinary calculi as a consequence of their metabolic effects on urinary pH and/or the excretion of calcium, phosphate, oxalate, citrate, uric acid, or other purines (Daudon et al. 2018). The clinical characteristics of the phenotype for nephrolithiasis include crystalluria, nephrolithiasis, and the ultrasound finding of a stone, with or without obstruction. Imaging is often the only method to detect nephrolithiasis but may not be available in all cases (Mehta et al. 2015). The common drugs that cause nephrolithiasis are shown in Table 6.6. Considering the high incidence of nephrolithiasis in the general population, it is important to identify the temporal relationship to the drug and analyze the stone composition, if available.

Table 6.6 Drug-induced Nephrolithiasis

Drug-induced Renal Calculi formation (Daudon et al. 2018)	Drug-induced, Purine Containing, Radiolucent renal Calculi (Daudon et al. 2018)	Drug-induced, calcium-containing, radiopaque renal calculi (Daudon et al. 2018)
Aciclovir, Allopurinol, Amoxicilin, Amphotericin B, Ampicillin, Amprenavir, Antrafenine, Atazanavir, Ceftriaxone, Ciprofloxacin, Clays (used as antidiarrhoeal drugs) Colloid silica, Darunavir, Enfavirenz, Ephedrine, Felbamate, Floctafenine, Flumequine, Foscarnet, Glafenin, Guaifenesin, Indinavir, Magnesium trisilicate, Mesalazine, Methotrexate, Nitrofurantoin, Norfloxacin, Oxolinic acid, Phenazopyridine, Pipemidic acid, Primidone, Pseudoephedrine, Raltegravir, Ritonavir, Sulphadiazine, Sulphafurazole, Sulphaguanidine, Sulphamethoxazole, Sulphaperine, Sulphasalazine, Trianterene	Ammonium chloride, Allopurinol, Benzodiarone, Benzoromanone, Nimesulide, Phosporic Acid, Sodium Phosphate, Tienilic acid	Acetazolamide, Ascorbic Acid (overdosing) Calcium / Vitamin D Supplements, Dexametahasone (premature neonates), Diclhorphenamide, Dorzolamide, Furosemide, (nephrocalcinosis in premature neonates) Methazolamide, Sodium Bicarbonate or others carbonate salts, Topiramite, Zonisamide

6.5.5 Composite Phenotypes

In clinical practice, regardless of the phenotypes having distinct characteristics, a patient may develop more than one phenotype. A patient that develops drug-induced crystalluria and nephrolithiasis could potentially develop AKI from obstruction or AIN. The panel for phenotype standardisation of drug-induced kidney disease considered that the combination of phenotypes is possible. In this situation, each of the phenotypes would therefore need to be evaluated independently, to establish a relationship with the drug exposure (Mehta et al. 2015).

6.6 Causality Assessment

The adverse drug reaction causality scoring tools, such as the Naranjo algorithm, exist for general reactions; however, these algorithms have not been evaluated for causality scoring of DIN. Challenges in the causality assessment include multidrug exposures and concurrent AKI risks. For example, the risk of DIN by antimicrobial drugs in sepsis, would be enhanced by hypotensive episodes and exposure to contrast agents. Considering these situations, it is recommended that each causal drug be evaluated, individually, with respect to their possible contribution to the phenotype; the underlying risk factors should also be assessed. Considering patients in polypharmacy with multidrug exposure, each causal drug should be ranked or classified as a primary or a secondary agent. It is, however, difficult since these assessments are based on the individual presentation of the patient, and may reflect a substantial degree of subjectivity depending on the adjudicator's knowledge of DIN. The temporal relationship, magnitude and duration of effect, and the knowledge of the nephrotoxicity mechanism are also important factors that must be evaluated (Mehta et al. 2015; Awdishu and Mehta 2017).

6.7 Management of Drug-Induced Nephrotoxicity

Treatment of nephrotoxicity is dependent on the phenotype, severity of the injury and the therapeutic aim for which the drug was prescribed (Mehta et al. 2015; Awdishu and Mehta 2017). The decision to stop or reduce the dose of the offending drug, requires careful consideration of the risks versus benefit. Type A adverse drug reactions are dose-dependent toxicities, and are predictable based on the known pharmacology of the drug. This type of adverse reaction can therefore be alleviated by reducing drug exposure or by withdrawing the use of the drug; dose reduction may be sufficient to mitigate the injury (AKI induced by amphotericin B or tacrolimus). Type B reactions are unpredictable based on the known pharmacology of the drug and dose-independent toxicities. Type B DIN, which is idiosyncratic, will

require the discontinuation of the offending drug and careful observations. Severe injuries or type B reactions frequently require longer periods of time for improvement, and may not completely resolve (Awdishu and Mehta 2017).

After the identification of DIN, the patient should be monitored carefully, and a daily assessment of SCr and urine output be conducted. This is because changes in kidney function may lead to further injury or a lack of a clinical cure for the infections. Other risk factors or kidney injury should be addressed such as, but not limited to, hypotension, hyperglycaemia, anaemia, and minimisation of nephrotoxins or drug interactions, which may contribute to the injury. Exposure to concurrent nephrotoxins should be reduced, if possible (Awdishu and Mehta 2017).

Dose adjustments, to ensure kidney function, should be performed for the other drugs that the patient is receiving. Therapeutic drug monitoring should be employed and continued even after drug discontinuation in situations where supra-therapeutic concentrations are documented during the injury (Awdishu and Mehta 2017). Clinical pharmacist consultation can improve the achievement of target concentrations and improve clinical cure rates. To prevent repeated exposures and subsequent injuries during future hospitalisation, in addition to the improvement of transition of care, it is imperative to document the event. Patients should be informed of DIN to empower them to advise other healthcare providers of their susceptibility to the drug (Awdishu and Mehta 2017; Kane-Gill and Bauer 2017).

Most cases of DIN are reversible, with few patients requiring renal replacement therapy. The use of renal replacement therapy for DIN is two-fold. First, dialysis can be utilised to remove the offending drug and minimise the ongoing damage. Additionally, dialysis can be utilised to support renal function, to allow recovery (Awdishu and Mehta 2017).

The decision to begin renal replacement therapy is complex and is generally reserved for severe injuries or cases where the drug toxicity may be mitigated by removal using dialysis (e.g. aminoglycosides, lithium, meropenem, vancomycin) (Awdishu and Mehta 2017; Susla 2009; Honore and Spapen 2018). The clinical pharmacist should identify the nephrotoxic drugs that can be removed by a renal replacement membrane, to analyse, with the prescriber, the need for a dosing adjustment.

6.8 Management of Nephrotoxic Drugs During Acute Kidney Disease

The management of drugs used by patients is important, and should begin immediately after the identification of DIN, and continue until recovery. The phenotype of drug-associated AKI occurs in approximately 25% of critically ill patients. Therefore, drugs function as a frequent cause of AKI, and the associated consequences are severe. The rates of non-recovery, dialysis, dependence and/or the mor-

tality that induce AKI, are similar to AKI from other aetiologies (40–50%) (Ostermann et al. 2018). Guidelines are available for the drug management of AKI (Matzke et al. 2011); however, little is known of patients with acute kidney disease (AKD) (Ostermann et al. 2018). AKD is defined as a condition in which the renal pathophysiological processes are still ongoing, with AKI stage 1 [as defined by KDIGO criteria] present, ≥ 7 days after an AKI-initiating event (Matzke et al. 2011)

Recommendations for drug management in AKD, following a modified Delphi method, were published in the Report of the Acute Disease Quality Initiative XVI consensus conference. With regards to nephrotoxicity, the group highlighted that medication regimen assessment or introduction of medication during the AKD period, should consider the nephrotoxic potential. Strategies to avoid adverse drug reactions in AKD should seek to minimise adverse events from overdosing and nephrotoxicity. To guide the medication regimen assessment, it is suggested that renal diagnostics tests, therapeutic drug monitoring, and a dynamic monitoring plan, including repeated serial assessment of clinical features, be utilised (Ostermann et al. 2018).

Following the Report of the Acute Disease Quality Initiative XVI Meeting, the initiation of use of a nephrotoxic drug should be avoided in these situations (Ostermann et al. 2018): (i). patient has known risk factors of kidney injury (i.e. elderly, a previous AKI episode, diabetes mellitus, CKD, proteinuria, hypertension) (Kane-Gill and Goldstein 2015; Kidney Disease 2012; Cartin-Ceba et al. 2012); (ii). a suitable and less nephrotoxic drug is available. (iii). a nephrotoxic drug is considered non-essential; (iv). patient is already receiving a nephrotoxic drug and there is concern of a pharmacokinetic or pharmacodynamic drug interaction; (v). the aim of duration of the drug therapy is chronic and the initiation of drug use can be delayed until after the AKD episode; (vi). biomarker indicates renal tubular injury is impending; (vii). biomarker predicts risk of drug accumulation; and (viii). there is a concern, from a lack of appropriate follow-up, of serum creatinine and/or therapeutic drug concentration monitoring (Ostermann et al. 2018).

To discontinue a nephrotoxic drug, it is essential to evaluate the causal relationship as this indicates if the drug is a potential cause of AKI or AKD. Other recommendations prior to discontinuation include: availability and suitability of a less nephrotoxic drug, a nephrotoxic drug is considered non-essential, and a biomarker indicates that a renal tubular injury has occurred (Ostermann et al. 2018).

Regular monitoring of functional status while taking a nephrotoxic drug is crucial, as either increasing or decreasing the dose may be necessary. Thus, to improve the management of a nephrotoxic drug, the clinical pharmacist should use evidence of the dosing guidelines. When possible, the duration and exposure to a dose of nephrotoxic drug should be minimised (Ostermann et al. 2018). In situations that nephrotoxic drug administration is essential, it is important that the clinical pharmacist monitor and manage the subsequent adverse drug events (Kane-Gill and Bauer 2017; Ostermann et al. 2018).

6.9 Conclusion

DIN is an important and potentially modifiable renal adverse drug event. Identifying the medications that induce nephrotoxicity is essential in clinical practice. Therefore, it is required that the clinical pharmacist understands which patients are at the highest risk of DIN and implement the judicious use of nephrotoxic medications and frequent monitoring, particularly when a combination of nephrotoxic drugs is used. For patients with confirmed DIN, the use of nephrotoxic drugs should be greatly avoided to aid in renal recovery and prevent recurrent DIN.

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