Chronic Kidney Disease and Renal Replacement Therapy – An Overview for the Advanced Clinical Practitioner

Introduction

Chronic Kidney Disease (CKD) is a common, globally significant condition, with associated significant mortality and morbidity. Globally, CKD has been ranked as the 18th most common cause of death, but with a disproportionately high loss of years of life associated with the condition (Jha, 2013). CKD is commonly classified according to GFR (Glomerular Filtration Rate), with lower GFR corresponding to worse disease, and CKD 5 representing ‘end stage’ kidney disease (ESKD). For many Advanced Clinical Practitioners (ACPs), CKD, dialysis and transplantation can be areas of clinical under confidence due to their perceived specialism. This article examines definitions of CKD, some key considerations in the clinical approach to a patient with CKD, including history and examination findings, and provides a brief overview of renal replacement strategies for the patient with ESKD. The article concludes with an overview of prescribing considerations for the patient with CKD.

Defining CKD

“CKD is defined as abnormalities of kidney structure or function, present for > 3 months, with implications for health.”

(KDIGO, 2013, p 5)

The broad definition of CKD proffered by the ‘Kidney Disease Improving Global Outcomes’ group (KDIGO) has been widely adopted, including in UK guidance (NICE, 2021), and it is important to recognise that we generally consider this to be a progressive process. The rapidity of progression will vary between individuals, dependent upon underlying aetiology and co-morbidity factors. This is in opposition to a diagnosis of Acute Kidney Injury (AKI) where there is an acute decline in kidney function. Whilst an in depth consideration of AKI is beyond the scope of this article, it is recognised that AKI, especially when presenting on top of already present chronic kidney disease, raises important safety issues, particularly with regard to medication management, so this is briefly addressed within the medication section below.

The definition adopted by KDIGO reflects that patients may be classified as having CKD with a ‘normal’ GFR (> 90 ml/min/1.73 m²). This may include: albuminuria (may be expressed as proteinuria); urine sediment abnormalities; electrolyte abnormalities due to tubular disorders; histological changes; structural change detected on imaging; history of kidney transplantation (KDIGO, 2013). Recognition of the potential for a diagnosis of CKD in the context of a ‘normal’ GFR is clinically important, as CKD confers a significantly increased risk of mortality and cardiovascular disease even in patients without decline in their GFR (Matsushita et al, 2010).

Fulfilling criteria for a diagnosis of CKD does not indicate the cause of renal dysfunction, and patients will need further investigation to ensure the timely introduction of any therapies directed at optimisation of underlying pathological conditions. Key significant causes of CKD are listed in Table 1. Further detailed consideration of specific aetologies
is beyond the scope of this article, though diabetes, as the leading cause for CKD in the UK, is briefly reviewed in Figure 1.

Having defined the presence of CKD, it can be classified, according to GFR, within a five stage classification promoted by KDIGO (2013). This five stage classification represents a progressive worsening of kidney function, with stage five corresponding to ESKD. Stages of CKD are presented in Table 2. Notably, earlier stages of CKD are likely to be symptomless, though recognition of abnormal renal function is important in order to be able to monitor appropriately.

Although the terms ‘GFR’ and ‘eGFR’ (estimated GFR) are often used as directly synonymous, there may be variation in these measures, with GFR reflecting a direct measurement of renal function through one of several methods, and eGFR reflecting a derived, estimated measure of renal function based on measured serum Creatinine. In clinical practice eGFR is routinely used, as this is reported from most biochemistry laboratories as part of a readily available blood assay.

While eGFR is routinely utilised, multiple potential pitfalls in interpretation of eGFR exist. Not least among these is the fact that multiple equations may be used for the calculation of eGFR in different settings, with significant variability among them. For example Trevisani et al (2020) compare accuracy of eight different equations, concluding that the degree of variance between eGFR and measured GFR increases as renal function deteriorates. Other sources note the development of over 50 different equations to estimate eGFR (Luis-Lima and Porrini, 2017). Additionally, in extremes of body mass, or following intense physical activity or trauma, or when muscle mass is decreased (for example in anorexia or sarcopaenia), eGFR may be unrepresentative of true renal function (Luis-Lima and Porrini, 2017; Racz et al, 2012). Such pitfalls or sources of error in eGFR estimation should be understood and taken into consideration in the clinical use of such measures (Thomas, 2019; Renal Association, 2020).

Beyond staging of CKD according to eGFR, further classification of an individuals' renal function, according to level of albuminuria, should be applied, again, as per KDIGO guidance (2013). Measurement of Albumin:Creatinine Ratio (ACR) is advised for individuals with diabetes, and for those with a GFR less than 60 ml/min/1.73m². Utilising ACR rather than protein:creatinine ratio (PCR) is suggested, as the latter is less sensitive for low levels of proteinuria (NICE 2020). Measurement of ACR is achieved through laboratory testing of urine samples, with figures of greater than 3mg/mmol considered clinically significant (NICE 2020). The use of reagent testing strips is advised against unless specifically capable of detection of low levels of albumin.

Applying a quantification of albuminuria alongside GFR allows application of a framework supported by national guidance, with suggested frequency of follow up and actions according to risk of progression of disease (See table 3) (NICE, 2021). Essentially, increasing albuminuria and decreasing GFR may both be considered markers of increased risk, with corresponding increasing levels of surveillance and follow up suggested. UK guidance follows that of KDIGO, with NICE adopting the same criteria in their most recent Clinical Guideline (NICE, 2021). A key message is that while increased ACR and decreased eGFR both independently confer increased mortality, if present in combination there is a multiplicative effect on the risk of mortality (Kerr, 2012; Matsushita et al, 2010;
Within England alone, there are around 1.8 million individuals with diagnosed CKD, with an estimated further million undiagnosed (Kerr, 2012). Other studies, utilising self-reported measures, cite a prevalence of CKD in England of approximately 2%, similar for both men and women (NHS Digital, 2017). Both prevalence and severity of CKD increase with age, with 46% of over 75 year olds having some degree of kidney disease (NHS Digital 2017). The overwhelming majority of individuals diagnosed with CKD will be managed in a primary care setting. Notably, only a small percentage of patents diagnosed with CKD will go on to progress to ESKD, suggested at 1% and 20% of patients with Stage 3 and 4 CKD respectively (Kshirsagar et al, 2008). However, even in the absence of disease progression, a significantly increased risk of death has been demonstrated as a direct association with diagnosis of CKD (Kerr, 2012). One UK study found a 69% mortality at a mean follow-up period of 5.5 years, with 46% of deaths occurring from cardiovascular causes (Dreyer, Roderick, Mullee and Rogerson, 2003). Interestingly, and reinforcing the notion of limited progression to ESKD, only 4% of this cohort were established on a Renal Replacement Therapy by the end of follow up. UK wide figures support such limited progression to renal replacement therapy (RRT). In 2018 there were 8000 new patients commenced on some form of RRT (Haemodialysis (HD) / Peritoneal Dialysis (PD) / Transplant) and about 26,000 people receiving HD or PD (UK Renal Registry, 2018), suggesting < 0.5% of diagnosed patients progressing to RRT on an annual basis.

It should be recognised that although UK wide figures are cited above, the incidence and prevalence of CKD varies greatly depending upon the population studied, including ethnic group and socio-economic class (Mathur, Dreyer, Yaqoob and Hull, 2017; Udayaraja, Pruthi, Casula, Roderick, 2013).

**Clinical Assessment of the Patient with CKD**

Clinical findings from assessment of the patient with CKD will depend upon the stage of CKD experienced, with many patients having few or no symptoms from their condition and thus leading to late presentation (NICE 2021). Where symptoms are experienced, this clinical manifestation of renal disease has been referred to as ‘the Uraemic Syndrome’, reflecting the accumulation of urea, due to decreased renal clearance of this waste product, as one of the key drivers of symptoms (Dobre, Meyer, Hostetter, 2019; Vanholder et al, 2018). Broadly speaking, patients at or approaching End Stage Kidney Disease (CKD stage 5) can be expected to experience a greater burden of symptoms and are unlikely to be symptom free. Consideration of the overall impact of symptoms experienced is one of the key drivers to commence RRT, discussed further below.

In examination of a patient from a renal perspective, key questions to be answered relate to fluid status, and evidence of any co-existent pathology which may be contributing to renal dysfunction (for example hypertension). In the newly diagnosed patient with CKD, other findings in the history or examination may prove useful clues to guide further investigation, management and secure an underlying diagnosis. For example, a hearing aid user presenting with progressive CKD may prompt consideration of a diagnosis of Alport syndrome (a genetic disorder of the glomerular basement membrane, also affecting cochlear and ocular basement membranes, of variable genetic transmission and presenting commonly with haematuria as the first symptom (Kashtan, 2021). Similarly,
knowledge of long-standing diabetes (or stigmata of the same) may support a diagnosis of diabetic nephropathy.

Multiple, non-specific symptoms such as, but not limited to, fatigue, nausea, decreased appetite, pruritus and spontaneous bruising are common in the patient with progressive CKD (Dobre, Meyer, Hofstetter, 2019). The insidious nature of symptom onset means they may not be mentioned by patients unless specifically explored. Hypertension will be present in a majority of patients with CKD (cited at 60-90% of patients dependant on stage and underlying aetiology of CKD) (Ku, Lee, Wei and Weir, 2019). Nocturia is a common early sign of CKD owing to a decreased ability to effectively concentrate urine in the ailing kidney. Nocturia has been reported as having a prevalence as high as 64% in patients with CKD, with self-reporting of this symptom identified as an independent indicator of progression to ESKD (Lombardo, Tubaro and Burkhard, 2020). Fatigue, breathlessness or altered breathing patterns are common and may relate to a variety of causes, including renal anaemia, fluid accumulation or metabolic acidosis.

Patients presenting with advanced ESKD may demonstrate symptoms of uraemic encephalopathy, manifesting as confusion, agitation, or other cognitive dysfunction, potentially with associated asterixis (a flapping tremor of the outstretched, dorsiflexed hands). It is likely to be seen in its more severe forms when eGFR falls below ~ 15ml/min, though cognitive change may be evident with an eGFR in the 40-60ml/min range (Olano, Akram, Bhatt, 2021). This phenomenon may be present in up to 60% of patients with CKD (Olano, Akram, Bhatt, 2021), and has been demonstrated in the majority of the haemodialysis population by some studies (Murray et al, 2006). As a diagnosis of exclusion, if uraemia encephalopathy is suspected, alternate causes for these symptoms would need actively excluding (for example: infection; hepatic encephalopathy; intra-cranial event; hypoglycaemia; hypertensive encephalopathy and others).

In the case of ESKD, patients will often appear generally unwell, with signs of anaemia, and a pallid complexion (sometimes described as ‘lemon-yellow’) (Innes, Dover, Fairhurst and McLeod, 2018). As a result of CKD and associated uraemic accumulation, uraemic pruritus may be present. This results from a combination of factors including drying of the skin, abnormal calcium and phosphorus metabolism, and general toxin accumulation (Vyas, 2010). On examination, scratches and excoriation may be evident, as may bruising, at least partly attributable to the effect on platelets of the uraemic milieu. CKD and particularly ESKD patients are at significantly increased risk of both bleeding and thrombotic complications due to a variety of complex pathophysiological interactions. Effective dialysis may partly mitigate bleeding risk. See Lambert (2016) and Schrauben and Berns (2019) for wider discussion on this topic. Although now rarely seen in a UK context, ‘uraemic frost’ on the skin is a marker of severity of disease (Madeux, Pons, Elkoun, Thiery, 2016).

A cutaneous manifestation of renal disease which should not be missed is rash, potentially consistent with a vasculitic cause. This autoimmune condition may present cutaneously as a palpable, purpuric rash, which may, in the presence of deranged renal function, signal kidney involvement in the disease process. This will be confirmed by testing for specific antibodies (ANCA - Anti Neutrophil Cytoplasm Antibodies). A potential new diagnosis of ANCA vasculitis will generally involve referral to renal specialists for ongoing management. Further investigation will normally involve ultrasound assessment of the kidneys, and often progression to renal biopsy, with management dependant upon degree of renal
impairment, chronicity of onset, and biopsy findings (McClure and Jones, 2018).

Examination of the hands and arms may demonstrate a variety of findings. Nail changes include leukonychia, Muerhckes nails (bands of pale striations), Beau’s lines, or ‘half and half’ nails, with lighter bands proximally (Alston and Burns, 2011). Assess for splinter haemorrhages as potential markers of endocarditis. Assessing warmth and perfusion of both hands may provide useful information. For example, the presence of an Arterio-Venous (AV) fistula for dialysis access may cause diminished circulation (potentially vascular steal syndrome (Morris, Knechtle and Marson, 2020), noted in the ipsilateral hand as coolness or paller. Conversely, hyperaemia due to increased flow may be present, with flushing and warmth of the ipsilateral hand in comparison to the non-fistula arm. Altered sensation may be consistent with peripheral neuropathy due to diabetic complications. There may be evidence of finger prick testing in the diabetic patient also.

Blood pressure testing will commonly demonstrate hypertension in the newly diagnosed patient, or potentially normo-tension in patients maintained on anti-hypertensive agents. Attempt to ascertain individual patients’ baseline blood pressure, from third party sources if necessary, as patients may experience large shifts in BP from baseline but still fall within ‘normal’ parameters (such as those outlined on early warning system documentation). As noted earlier, renal hypertension is very common (Ku et al, 2019), and, due to the complex and multi-factorial nature of its pathophysiology, may be particularly refractory to treatment. It will therefore not be uncommon to find patients with CKD maintained on three or more pharmacological agents to manage hypertension. Renal hypertension is a significant topic of study in its own right with multiple mechanisms contributing, including: overstimulation of the sympathetic nervous system; sodium retention; increased renin-angiotensin-aldosterone system (RAAS) activity; increased intracellular calcium levels and potential contributions from drugs such as erythropoetin administered to mediate the effects of renal anaemia (Ku et al, 2019). The difficulties are compounded by the fact that CKD contributes to development of hypertension, while hypertension may also play a major role in development of CKD. Blood pressure control is thus key to slowing progression of CKD, with target systolic blood pressure of less than 140mmHg advocated for adults with CKD and ACR < 70mg/mmol, and tighter control, with a target of less than 130mmHg for adults with CKD and an ACR >70mg/mmol (NICE, 2021). Due to the above factors, a multimodal approach to management of renal hypertension is common, with drug treatments aimed at key targets in the contributing mechanisms outlined. United Kingdom guidance for patients with CKD (NICE, 2021) is aligned to population wide guidance (NICE, 2019) which promotes a step-wise approach to pharmaceutical management of hypertension, commencing with an angiotensin-converting enzyme (ACE) inhibitor. Notably, patients with CKD and diabetes, or CKD and proteinuria >70mg/mmol, even in the absence of hypertension, should also be offered an ACE inhibitor due to the potential improvement in proteinuria conferred by the medication. As discussed below, many medications need careful consideration in the CKD population, and ACE inhibitors are a good example of a medication needing careful introduction, due to potential deleterious effects on potassium regulation and renal function. Therefore, patients commenced on ACE inhibition, or having had a dose increase, should have blood rechecked between 1-2 weeks from the change, in order to assess for this (NICE, 2021). A decrease in eGFR of < 25% of baseline, or increase in creatinine of < 30% is acceptable according to national guidance (NICE (a), 2021). Variation greater than these limits should prompt consideration of change of therapy and investigation for other potential contributing factors, including potential ‘unmasking’ of underlying reno-vascular
Assessment of the arms may reveal the presence of an arterio-venous (AV) fistula, the accepted definitive choice of vascular access for the haemo-dialysis (HD) patient. This will normally be either radio-cephalic (radial artery to cephalic vein at the wrist), or brachio-cephalic / brachio-basilic at the elbow. The fistula is truly a lifeline for the HD patient, and they will generally be highly attuned to changes in it’s condition. Although multiple surgical sites of fistula formation are available, loss of options for HD access in the context of multiple failed fistulae may represent a treatment limiting problem. Consequently, patients are trained not to allow any interventions to be performed on their fistula arm as these may jeopardise flow and patency. This includes blood pressure measurement, venepuncture and cannulation. Many HD patients will elect to wear an alert bracelet, silicone band or similar to alert first responders in the event of becoming unwell. For patients in hospital, an allergy band or similar should be applied to the fistula arm to reinforce this.

Fistulae should be assessed for pulsatile flow (a palpable thrill) and the presence or absence of a bruit through auscultation. Raising the arm while palpating will demonstrate any ‘collapsing’ of the fistula pulsation, supporting a diagnosis of hypovolaemia. Occasionally a fistula will develop to such an extent as to contribute to a heart failure symptomatology, and should be considered in the patient with heart failure symptoms (Stern and Klemmer, 2011). Referral for formal ultrasound assessment may be indicated in such situations, with surgical reduction of flow through the fistula potentially indicated.

Particularly in the context of systemic illness, decreased blood flow may lead to the failure of a fistula through thrombus formation. Dialysis patients will routinely check their own fistula and, if any concerns are raised, their first point of contact will normally be their renal unit for further investigation (ultrasound assessment as first investigation commonly) and consideration of alternate access to facilitate haemodialysis. A general assessment of the ESKD patient should also seek evidence of previous access formation attempts. This will be demonstrated through scarring consistent with alternate fistula locations and corroboration from the patient.

Jugular Venous pressure or JVP is routinely examined as a marker of fluid status, reflecting right atrial pressure and thus utilised as a surrogate marker of overall ‘filling’ status of the patient. If a patient is significantly fluid overloaded the practitioner may expect to find elevated JVP. As considered below, such an indication may trigger early consideration of initiation of dialysis in an oliguric ESKD patient. However, in interpreting JVP findings, it should be noted that there is a relative, perhaps surprising, dearth of literature in relation specifically to JVP in CKD. A small study of PD patients demonstrated poor correlation between clinical JVP findings and fluid overload in this patent group (Garfinkle and Barton, 2016). Regardless, assessment of the JVP remains an established component of a comprehensive renal examination. For novice practitioners, it can be challenging to convincingly ascertain the JVP, so confirmation with an experienced practitioner may be useful until confident. Commonly the JVP is assessed with the patient reclined at 45 degrees to start, and the head turned away from the observer, but with the neck muscles relaxed. A normal (‘non-elevated’) JVP will be seen with point of maximal pulsation no more than 4 cm vertically above the sternal angle. Failure to see the JVP at 45 degrees should prompt progressively flattening or elevating the patient until JVP can be seen. Confirmation of JVP may be via a variety of

disease (i.e. renal artery stenosis) (NICE (a), 2021).
techniques. It should be: impalpable (in comparison to carotid artery pulsation); occludable; demonstrate a double pulsation (assuming sinus rhythm); demonstrate respiratory variation in amplitude; and may be accentuated through firm pressure over the abdomen (abdomino-jugular reflux) (Innes et al, 2018; Magee, 2018).

Key facial signs to consider include anaemic changes such as pallor (best assessed in the mucous membranes of the lips and conjunctivae (Innes et al, 2018)). If anaemia is suspected, this should be confirmed through testing of haemoglobin levels, then further investigated with regard to whether this reflects anaemia attributable to CKD. It is suggested that a haemoglobin level of less than 110g/l, or symptoms attributable to anaemia, in a patient with an eGFR of < 60ml/min/1.73m² should prompt further investigation (NICE, 2015). Investigations will normally include measurement of serum Iron levels as well as ferritin and transferrin saturations, with interpretation of these results suggesting best course of treatment. Common approaches to management of anaemia in CKD will include supplemental iron (if deficient), and commencement of erythropoietic stimulating agents (ESA), followed by ongoing monitoring and dose titration (NICE 2015).

Assessment of mucous membranes is also included as a component of overall fluid assessment, with moistness or dryness being a somewhat subjective finding. Presence of xanthelasma may suggest hyper-lipidaemia as a modifiable contributor towards cardiovascular complications of CKD. Although uncommon in adults, facial oedema may be a marker of generalised hypoalbuminaemia, particularly in nephrotic syndrome (lower limb / dependant oedema being more common).

Cardiac, abdominal and respiratory components of the clinical examination have been described in detail in earlier articles in this series, so are not revisited fully here, though some specific renal considerations are outlined.

Auscultation of heart sounds may reveal an ejection systolic murmur, audible throughout the praecordium, related to AV fistula flow. A third heart sound (‘S3’) may be heard and would add support to any suspicion of volume overload (Ramani and Webber, 2017). Of note, the ability to detect S3 on auscultation has been strongly correlated to level of experience of practitioner (Marcus et al, 2006). Uraemic pericarditis is a significant concern in the ESKD patient, and may be appreciated as a pericardial friction rub on auscultation. Left Ventricular Hypertrophy (LVH) is common in the chronically hypertensive patient, and may be suspected in the presence of a displaced apical beat or heaves. Assessment of the praecordium may demonstrate scars of previous line insertion sites. Many patients will have required temporary access, either emergently, or as a bridging measure to allow maturation of fistulae. Scars from either temporary central venous access catheters or tunnelled central venous catheters (a specialist dialysis catheter with longer potential dwell time) may be consistent with line placement to any of the large upper abdominal vessels, with subclavian and internal jugular sites perhaps being the most common. Finally, diminished heart sounds, elevated JVP, tachycardia and hypotension are potential markers of cardiac tamponade, a long recognised cardiac complication of the uraemic condition (Bataille et al, 2015; Baldwin and Edwards, 1976).

Examination of the chest may reveal, deep, sighing respirations (Kussmaul’s breathing), as a compensatory response to the metabolic acidosis of CKD. Fluid accumulation and hypoalbuminaemia may lead to clinically appreciable pleural effusions and basal
inspiratory crackles. While examining the posterior chest, it is customary to assess for any sacral fluid. This manifests in a dependant fashion as a 'sacral pad' with pitting oedema.

Abdominal examination follows the usual pattern, assessing visually for any asymmetry (potentially arising from large, poly-cystic kidneys or the presence of renal transplant graft in left or right iliac fossa), or swellings. A suprapubic, smooth, central swelling may indicate a distended bladder, a potentially readily remediable cause of acute deterioration in function in CKD patients or patients presenting with new derangement in kidney function. The examiner will not be able to ‘get below’ a palpable bladder, and palpation will make discomfort worse in the patient with acute urinary retention. In this situation, urinary catheterisation will normally be indicated and should result in resolution of symptoms. Multiple scars may be noted, which may be prominent or subtle. Lower abdominal right or left iliac fossa scars may correspond to previous renal transplantation, in which case a graft kidney should be palpable and non-tender in healthy states. Graft tenderness, either on palpation or spontaneously, warrants further investigation (normally via renal graft ultrasound in the first instance).

Native kidneys are not routinely removed for renal transplantation, but very large, or recurrently infective, or bleeding, polycystic kidneys may have been removed prior to or post-transplantation (or in non-transplant patients for similar indications). Increasingly, nephrectomy is performed laparoscopically, even for large polycystic kidneys, so laparoscopic surgery scars should prompt suspicion for potential nephrectomy (Eng, Jones, Cannon and Marvin, 2013). Open nephrectomy scars tend to be large, curvi-linear and extend from flank to the lower costal margins of the posterior abdomen.

For patients undertaking peritoneal dialysis (PD) a ‘Tenckhoff catheter’ will be present on the anterior abdominal wall, positioned to avoid interference with clothing and taking account of body habitus. The abdominal wall exit site should routinely be inspected for any evidence of infection. Many ESKD patients may have trialed PD at some point, and perhaps been transitioned to HD, or transplanted, in which case the catheter will have been removed, but small scars may be evident.

The technique of kidney palpation is best learnt by direct demonstration, but involves ‘ballotting’ of the kidneys between both hands, at the renal angles, with one hand anterior and one posterior, and the kidney gently mobilised back and forth between both hands. Kidneys may not be palpable, dependent on body habitus, but if felt, they should be smooth, mobile and non-tender in healthy states. Renal angle tenderness on attempted palpation of kidneys is suspicious for ascending infection (pyelonephritis), stone disease, obstruction or abscess. Large, irregular kidneys may represent polycystic kidney disease, and accurate family history may be helpful in corroboration. Auscultation of the abdominal vessels, and over the kidneys, may demonstrate bruits, suggesting turbulent flow and potential vascular disease, potentially supporting a differential diagnosis of reno-vascular disease (Ku, Lee, Wei and Weir, 2019).

Finally, assessment of the lower limbs may demonstrate pitting oedema, consistent with hypoalbuminaemia. This should be quantified by extent, eg ‘pitting oedema to knees’. Assessment of peripheral pulses, and exclusion of clinical signs of DVT, should also be undertaken. Peripheral neuropathy may be evident, dependent on underlying disease and co-morbidity.

Renal Replacement Therapies (RRTs)
The appropriate timing of initiation of renal replacement is a nuanced, individualised decision, in partnership between patients and their renal team. Commencement of the selected RRT modality is generally guided by the overall burden of symptoms experienced by the patient. For some patients, signs and symptoms such as difficult to manage fluid retention, hyperkalaemia, or severe uraemia may trigger more rapid initiation. In some cases, symptoms may not prove troublesome, in which case an eGFR of 5-7ml/min/1.73m² is considered a reasonable starting point for RRT (Tattersall et al, 2011; NICE, 2018).

Ideally, planning for RRT for CKD will have taken place in clinic settings prior to the need arising, based on the trajectory of decline of renal function, with national guidelines suggesting a year in advance of expected commencement (NICE, 2018). These discussions should focus on choice of modality of RRT as a patient and family centred decision, guided by the renal team and with thought given to lifestyle factors and individual patient ability to manage aspects of RRT themselves. This planning phase should include consideration of access for RRT, either in the form of PD catheter insertion or arteriovenous fistula formation with time allowed for healing and maturation of the fistula.

In ESKD the ‘Gold Standard’ of management may be considered renal transplantation, re-establishing normal or near normal renal function and independence from supportive intermittent RRTs (Kidney Care UK, 2021). However, for a variety of reasons, ESKD patients may not be suitable candidates for transplantation (for example: high co-morbidity burden, malignancy, advancing age, psycho-social factors, very highly sensitised immunological status). Even if identified as a potential candidate for transplant (and the default position for referrers should be to assume ‘transplantability’ until proven otherwise, ensuring an informed discussion with patients prior to commencement on RRT (NICE 2018)), the majority of patients will require a period of RRT in the interim. From a patient perspective, avoiding dialysis would be ideal, and as patients can be ‘activated’ on the transplant waiting list within 6 months of anticipated commencement of RRT, there is the possibility of ‘pre-emptive’ transplantation taking place (i.e. pre-dialysis). Where this does occur, it is often in the context of a live-donor transplant. The combination of Live donor transplantation to a pre-dialysis patient is likely to give the best possible outcome from the procedure. A detailed overview of renal transplantation is provided by Dunsmore (2019).

Alongside Kidney Transplantation, the two other main modalities of RRT available are PD or HD, and all options have advantages and disadvantages, summarised in Table 4. Both modalities are also considered in more detail below. Additionally, in acute or acute-on-chronic kidney injury, Continuous Venovenous Haemofiltration (CVVH) may be utilised, normally in an ITU or HDU context. Although dialysis will maintain life, we should not underestimate the toll that it takes on patient’s quality of life, as recognised by Goodman and Danovitch (2010):

“...fatigue and malaise persist... Progressive cardiovascular disease, peripheral and autonomic neuropathy, bone disease and sexual dysfunction are common... Rehabilitation, particularly vocational rehabilitation, remains poor.”

(2010, p 1)

This is perhaps not surprising when one considers that even well dialysed patients will only achieve in the region of 15% of the normal waste clearance of two healthy kidneys (Danovitch, 2010).
It should also be recognised that, for some patients, declining dialysis and opting instead for a ‘conservative’ care approach may be a preferable option (sometimes referred to as a ‘non-dialytic approach’) (Noble, Carswell, Walsh, 2019).

To illustrate some key differences, Alston (2013) quotes number of hospital attendance days at 4% versus 47% for conservative and HD approaches respectively, and also notes an average recovery time of 8 hours from each HD session. A conservative approach may be particularly worth consideration in patients of advancing age or with other co-morbidites which may make tolerating the demands of RRT challenging (for example severe cardiac or respiratory disease, dementia or cognitive decline). Of note, Verberne et al (2017) demonstrate equivalent self-reported quality of life measures between conservative care patients and those established on HD (though in a single centre study with a relatively small patient cohort). If a conservative approach is adopted, the patient will continue to be monitored by the renal team, with issues such as renal anaemia & mineral bone disorder still actively managed to optimise quality of life and independence, alongside close attention to management of symptoms arising from ESKD (Noble, Carswell and Walsh, 2019).

**Haemodialysis:**
Intermittent haemodialysis remains the standard therapy for maintenance of metabolic stability in ESKD patients. Patients will attend hospital dialysis units up to three times weekly (many patients may opt for ‘self-care’ in a hospital setting, or home HD for a select cohort, both options with additional training from renal expert staff).

Having had a fistula formed in preparation, it will be ‘needled’ to allow placement of 2 large bore cannulae, one nominally venous and one arterial, to allow flow of blood between the patient and the dialysis machine (figure 2). HD works to extract waste products and excess fluid from the blood across a dialyser membrane, and uses a contraflow of the dialysate against blood flow to provide a concentration gradient.

An average dialysis session may last around four hours. The duration of individual sessions is dictated by regular and careful pre- and post-session blood sampling to determine the URR (Urea Reduction Ratio), with most centres aiming to achieve a minimum ‘dose’ of 65% URR, and assessing this on a monthly basis. URR is utilised as a surrogate for a more complicated measure which relates to individual dialyser characteristics, the Kt/V for urea. Achieving higher URR is possible through longer treatment times, change to dialyser membrane, and changes to blood flow rates and dialysate flow rates (EdRen, 2021). Blood flow rate, and thus the efficiency of dialysis treatment, may be limited by type and adequacy of access and may prompt surgical revision of the fistula to improve this. Additional variables include the potassium and calcium concentrations of the dialysate fluid, bicarbonate concentration (to address academia of CKD), dialysed temperature and choice of anti-coagulation.

**Peritoneal Dialysis**
This form of dialysis requires insertion of a flexible dialysis catheter into the peritoneal space. The peritoneal membrane is then utilised as the ‘dialyser’ by instilling volumes of dialysis fluid into this potential space, via the PD catheter. Over the course of a ‘dwell time’, metabolic waste products diffuse from the peritoneal capillaries into the dialysis fluid. This fluid is drained off at the end of a cycle, and replaced with new, ‘clean’ dialysis fluid. Two main forms exist, CAPD (Continuous Ambulatory Peritoneal Dialysis), and APD (Automated Peritoneal Dialysis). APD utilises a machine with automated warming and exchange functions, and runs (generally) overnight, leaving patients free of dialysis during
the daytime. CAPD involves a series of manual exchanges, normally ~ four times daily, but normal activity may be undertaken whilst dialysis is underway. In contrast to HD, PD is often viewed as a ‘gentler’ form of RRT, with less extreme shifts in fluid and biochemistry and may be a better fit for patients with underlying cardiovascular instability.

Economic considerations
If transplantation is undertaken, as well as the significant patient centred improvements, there is also estimated to be a significant cost saving when compared to other modalities of RRT. A recent Swedish registry study estimates a €380,000 per patient saving over a ten year period for transplantation rather than HD, even if patients ultimately return to HD due to graft failure (Jarl, Desatnik, Peetz Hansson, Prütz, and Gerdtham. 2018). Others have been more guarded in their analyses, with a recent systematic review suggesting diminishing savings from transplantation in those over 60 years of age (Fu, Sekercioglu, Berta and Coyte, 2020).

Prescribing in Kidney Disease
Prescribing for the renal population can be challenging, (Joint Formulary Committee, 2020). There are multiple classes of drugs that are particularly problematic, some discussed briefly below. When considering initiating any new medication in a patient with CKD, it will be wise to adopt a ‘start low, go slow’ approach to minimise risks of adverse reactions, accumulation or impact on renal function. Increased frequency of monitoring may be a reasonable safety netting procedure. A low threshold should be adopted for discussion with renal specialist services and particularly with renal specialist pharmacists if any ambiguity exists. An important reference resource, readily to hand in any Renal unit, is the Renal Drug Handbook (Ashley and Dunleavy, 2018). Additionally, in the RRT population, consideration needs to be given to potential dialysability of medications (ie is the medication removed by dialysis), as this will impact timing of doses. For ACPs, knowledge of common drugs to avoid or prescribe with significant caution is crucial.

Examples of key medications and concerns for ACPs

Antimicrobials:
Nitrofurantoin is not recommended for patients with an eGFR < 60, due to risks of peripheral neuropathy and lack of effectiveness in treatment of UTIs due to poor urine concentration.
Gentamicin is generally avoided in acute kidney injury, and in acute-on-chronic kidney injury. It may be utilised in patients with advanced stages of CKD, but this will be via specific protocols.
Macrolide antibiotics may have a particularly potent effect on elevating serum levels of certain immunosuppressant medications (for example in the post-transplant patient), these interactions may drive nephrotoxicity and impact on function in this group.
Protocols for therapeutic drug monitoring of antibiotics may also be quite different in patients with ESKD, for example Vancomycin.

Non-Steroidal Anti-Inflammatory Drugs (NSAID’s)
Avoid if possible in all levels of renal dysfunction. Prolonged use may decrease native urine output irreversibly in patients on RRT. Chronic usage is associated with progression of CKD, and acute use with decrease in eGFR (normally reversibly) (NICE 2021). Use may be appropriate in select patients if no good alternatives exist, and following discussion.
Opioids
Opioids are generally not advised in CKD, due to potential for accumulation and significant adverse effects. Formulations considered at lower risk of accumulation include Fentanyl and Alfentanil, but these should be introduced at a low dose of an immediate release preparation and actively monitored for side effects. Avoidance of Modified Release formulations of opiates has been recommended. (Joint Formulary Committee, 2020; Whitworth and Thomson, 2021)

Diuretics and Antihypertensives
The optimal approach to the management of diuretic and anti-hypertensive medication will depend on the level of CKD and if any acute deterioration in kidney function is present. It should be recognised that patients with CKD are part of a wider group in whom these medications present particular risks of avoidable harm. Patients admitted to hospital or experiencing episodes of an acute intercurrent illness need particularly careful consideration.

The ‘Think Kidneys’ initiative has provided key guidance on a pragmatic approach to the stopping and restarting of these high risk medications (Think Kidneys, 2020), which has been widely adopted. This includes through the use of ‘Sick Day Rules’ to assist patients in optimising their own care.

A shared care approach to managing medication changes should be adopted wherever possible. Discussion with patients is a key factor in decision making around stopping / withholding / restarting medications and the attendant risks and anticipated benefits of each potential course of action.

Conclusions
Chronic Kidney Disease represents a broad spectrum of disease, from aysmptomatic abnormalities of biochemistry, through to multi-system manifestations of kidney disease, requiring intensive, three times weekly technological intervention to maintain life. CKD is common, and confers a high burden of morbidity and mortality. The ACP has a significant role to play regardless of the context of their practice. The majority of patients with CKD are managed in a primary care setting, where close attention to optimising underlying conditions and mitigating the effects of renal dysfunction is key to ensuring better outcomes. In secondary care, patients with CKD may present with a variety of complications of CKD, or novel pathology unrelated to CKD, but complicated by its presence. These patients all require a nuanced, multi-disciplinary approach in order to optimise their outcomes. Prescribing for this group may be challenging and close liaison with specialist services is recommended.

Key Points:

• Chronic kidney disease is a common condition which the majority of ACPs will encounter in their clinical practice.

• The role of the ACP in primary or secondary care may focus upon identifying the presence of CKD or preventing
further decline.

- Progressive renal dysfunction as a patient progresses through stages of CKD confers high morbidity and burden of symptoms, and significantly increases cardiovascular risk.

- Differing modalities of renal replacement therapy have particular advantages or challenges, and the ‘correct’ choice is a highly individualised decision for each patient.

- Prescribing for a patient with CKD is complex with dosing being affected by reduced kidney function or renal replacement therapies.

- Care of the CKD patient is a complex, interdisciplinary undertaking, with multiple professional groups playing key roles.

Reflective Questions:

1) Reflect upon common medication prescriptions which require caution for patients with CKD, how would you ensure safety if patients in your practice area require these medications?

2) Consider how to support a CKD patient who comes under your care, particularly in relation to end of life care.

3) Think about how you would support a patient who is facing a new CKD diagnosis.

4) What are the key elements to a person-centred approach when consulting with, and caring for a patient with chronic kidney disease?
References:


UK Renal Registry (2020) *UK Renal Registry 22nd Annual Report* – data to 31/12/2018, Bristol, UK. Available from renal.org/audit-research/annual-report


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