Oxford Textbook of Palliative Medicine

Chapter on “End-stage kidney disease”

Abstract

End-stage kidney disease (ESKD) accounts for 1-2% of all deaths. Ageing populations means that this proportion will grow steadily over the coming years. Symptom burden in ESKD exceeds advanced cancer, with added renal-specific symptoms, such as itch and restless legs. Pain and depression are also more prevalent. Many renal symptoms go under-recognized and under-treated, especially as they arise from co-morbid conditions, rather than the renal disease itself. The most useful intervention to address symptoms is regular assessment of symptoms, using a valid and reliable global symptom score. Pharmacological interventions to alleviate symptoms need to take account of the severe constraints on using renally cleared drugs, and the high risk of toxicity from accumulation of parent compound or metabolites. The population with ESKD has extensive palliative care needs, and need significant medical, nursing, psychological, and social care to address these as their illness advances towards the end of life.

Keywords

Kidney Failure, Chronic

Renal Dialysis

Palliative Care

Long term care

Withholding treatment

Introduction to end-stage kidney disease

End-stage kidney disease (ESKD), like end-stage cardiac or respiratory disease, leads eventually to death. However, unlike cardiac or respiratory disease, life-sustaining treatment in the form of dialysis is available. Initially, dialysis was a short-term treatment for patients with acute renal failure, with no provision of longer-term maintenance dialysis for patients with chronic renal failure. But the first dialysis programmes started in the 1960s and have steadily expanded in subsequent decades. At first, older patients or those with multiple co-morbidities were excluded, but more recently, the criteria for dialysis have been relaxed, and many more patients have been accepted onto dialysis programmes. For example, the prevalent UK renal replacement therapy population grew by 3.2% between 2015 and 2016, an annual growth rate which has been fairly consistent over the last 10–15 years (Byrne et al., 2018).This rise reflects several factors beyond increasing acceptance onto dialysis programmes, including an increase in the prevalence of renal disease, ethnic variations in renal disease, and an older population who are living longer.

Despite technical advances and changes in the way dialysis is delivered, it still remains a challenging treatment for many patients. Dialysis usually requires invasive procedures and then protracted treatment sessions three times each week. While some uraemic symptoms are relieved by dialysis, the overall symptom burden of those receiving dialysis remains high. For some patients with severe co-morbidity and short life expectancy, dialysis is either not feasible or is unlikely to improve quality or quantity of life. Other patients decide not to have dialysis, instead choosing conservative (non-dialytic) management of their renal disease. Their renal management then focuses on delaying progression of renal disease and controlling complications, alongside control of symptoms and psychosocial support as the disease progresses towards death. Symptoms are common for those with stage 4 chronic kidney disease (Almutary et al., 2016) (Senanayake et al., 2017), for those with end-stage disease on dialysis (Almutary et al., 2013) and those with end-stage disease not receiving dialysis (Brennan et al., 2015).There are, therefore, several groups of patients among those with ESKD who benefit from palliative care, whether that care is delivered by palliative care or nephrology clinicians, or by an integrated team which shares care across specialty boundaries. These patient groups are:

- those who choose or are advised not to embark on dialysis (conservative or non-dialytic management)
- those who are failing to thrive on dialysis, and who experience worsening quality of life and increasing symptom burden despite dialysis
- those who discontinue dialysis.

Epidemiology

A recent systematic review and meta-analysis of the global prevalence of chronic kidney disease confirms high prevalence; using only high quality studies only and weighting by number of participants, these authors estimated a global chronic kidney disease prevalence between 11 to 13% (Hill et al., 2016).

Only a small proportion of these will progress to ESKD, and to the time when a decision between conservative or dialysis treatment is required. Nevertheless, because the overall prevalence of CKD is relatively high, a large number of patients will reach ESKD.

Epidemiological studies also show that the prevalence of ESKD increases rapidly with advancing age. Stage 3–5 CKD is present in less than 1% of people under 35 years but is present in 40% of people over 75 years (Stevens et al., 2007). Initiation of dialysis is therefore much more frequent in the

elderly, and the proportion increases sharply among those over 65 years, peaks between 75 and 85 years, and only drops off after 85 years. This strongly age-related nature of ESKD means that the numbers with ESKD could be expected to increase further as the overall population in developed countries ages. However, the median age of prevalent UK patients on RRT at 59.1 years in 2016 has remained stable in the last few years - although it is notably higher than in 2005 when it was only 55.0 years (Byrne et al., 2018) Similarly, the United States Renal Data System (USRDS) reports that, while the standardized incidence rate of ESKD in the United States rose sharply in the 1980s and 1990s, this leveled off by 2006, and has now declined slightly since this peak. In 2016, there were 124,675 newly reported cases of ESRD in the US; the unadjusted (crude) incidence rate had risen; but the age-sex-ethnicity standardized rate had plateaued (US Renal Data System, 2016).

The exact number of patients who die of renal failure after conservative management (i.e. without receiving dialysis) is very difficult to ascertain, partly because of the lack of routinely collected data, but also because few population-based, rather than service-based, studies are conducted. Some patients with severe co-morbidity may never be referred to renal services. In reported series of patients known to renal services and managed in specialist low-clearance clinics, approximately 15–20% of those with declining renal function will follow a conservative pathway (Smith et al., 2003) (Murtagh et al., 2007e). In reality, this figure is likely to vary considerably between units depending on the demographics of the catchment population, and on how services are structured. A national observational study in Australia indicates that about 14% (one in seven) of patients with ESKD referred to nephrologists plan not to dialyse (Morton et al., 2012b). Comprehensive service provision with integrated palliative care needs to be improved to meet the demands of the ageing population. There have always been some patients managed conservatively, without dialysis, but practice has varied over time and between countries (Lambie et al., 2006), and between individual nephrologists (Kee et al., 2000), and it is only recently that there has been greater recognition of the conservatively managed group of patients, with systematic study beginning to be undertaken in order to address some of these very relevant questions.

Survival

There is limited evidence about the duration of survival of conservatively managed patients. First, although there have always been patients managed without dialysis, only recently has this group been recognized as a distinct population needing study. Second, it has been difficult to identify when survival should be measured from—patients may not require dialysis until well into stage 5 CKD, as they begin to experience worsening uraemic symptoms. And even if dialysis is planned, some will die of co-morbid disease before dialysis can commence, and others experience only a very slow decline in renal function, such that dialysis is not actually needed for some time. Third, documented survival may well reflect the demographics, co-morbidity, and local practice at any one renal unit, rather than mortality data that is readily generalizable.

There have been no prospective randomized trials which assess the benefit of dialysis versus conservative management in this population. The ethical challenges that this would raise are such that a randomized trial is unlikely to occur, and only observational studies are currently available to inform practice. Recently, Foote and colleagues reviewed all published evidence on survival among patients with ESKD, focusing especially on older patients (Foote et al., 2016). They identified 89 studies reporting on 294,921 older ESKD patients; however, these included survival data for only 724 patients who follows ‘non-dialysis’ management. Nevertheless, one-year survival for older patients treated with dialysis was 73.0% (95% confidence interval 66.3–79.7%), very similar to 70.6% (95% confidence interval 63.3–78.0%) for those who did not have dialysis. Two-year survival diverged between these two grops, but not for those with high levels of comorbidities. The main challenges in

interpreting this evidence for application into clinical practice are; lead-time bias; heterogeneity within both dialysis and conservative (non-dialysis) populations; and the striking absence of data from those managed without dialysis (Foote et al., 2016).

When there is no residual renal function, patients withdrawing from dialysis have a very short survival, with the evidence reporting a mean survival between 8 to 10 days (Murtagh et al., 2007a). Most patients will have a shorter survival than this, living just a few days after dialysis is discontinued, but the range is 1–46 days. If there is residual renal function, for instance, after a brief trial of dialysis, then survival can be very much longer (sometimes months), according to the level of residual renal function and the underlying disease processes.

Symptoms

There is increasing study of the epidemiology of symptoms in ESKD, although relatively less work studying optimal management of these symptoms. Work from the UK (Murtagh et al., 2007b) (Murtagh et al., 2007c) and Australia (Almutary et al., 2013) shows that each person with ESKD reports an average of about 12 or 13 symptoms with moderate or severe impact, with the most prevalent symptoms affecting more than 1 in 3 (individual weighted mean prevalence is reports for fatigue or tiredness as 71%, pruritus 55%, anorexia 49%, pain 47%, sleep disturbance 44%, anxiety 38%, dyspnea 35%, nausea 33%, restless legs 30%). Although it is clear that those with ESKD experience a high symptom burden, less is known about the symptom burden for people with CKD Stage 4 and for those with CKD Stage 5 receiving peritoneal dialysis. There is some work on the patient experience of conservative management (Noble et al., 2008) (Bristowe et al., 2019) (Selman et al., 2019), and the impact of it on families and carers (Ashby et al., 2005) (Low et al., 2008).

The symptom work that has been done shows that patients with conservatively managed stage 5 CKD have a high prevalence of symptoms (Murtagh et al., 2007c), similar in terms of overall burden to patients with advanced cancer, although with differences in the patterns of symptoms and the level of distress caused. Patients with ESKD are among the most symptomatic of any chronic disease group (Solano et al., 2006). Identifying and controlling symptoms is a high priority for patients and families (Steinhauser et al., 2000), and notably improves their quality of life (Weisbord et al., 2003). For those with ESKD, excellent symptom management becomes an increasingly high priority as the duration of time they remain dependent on chronic renal replacement therapy increases (Singer et al., 1999) (Steinhauser et al., 2000) (Almutary et al., 2016). It is also important to recognize that, while renal replacement therapy in the form of dialysis provides major benefit, including symptom relief, it will not always ameliorate or abolish symptoms and may sometimes contribute to them.

Prevalence of specific symptoms

Anxiety and depression

Anxiety is reported as occurring in 45-67% and depression in 36-59% of either stage 4/5 CKD or ESKD patients (Murtagh et al., 2007b) (Almutary et al., 2013). Much of this variation reflects variation in the populations assessed, the definitions of anxiety and depression used, and the instruments used to detect them. Screening tools, such as the Beck Depression Inventory, tend to identify a somewhat higher proportion (45–50%) of potential depression than diagnostic tools, depending on the level of cut-off used (Kimmel, 2001) (Wuerth et al., 2005). Patients managed without dialysis probably have similar levels of anxiety and depression, although evidence remains limited, and the prevalence of anxiety and depression likely increases over time (Murtagh et al., 2011). They have a high prevalence of the symptoms of feeling anxious or sad (63% and 50%, respectively), and 45% have depressive scores above the standard cut-off on the Geriatric Depression Scale (Murtagh et al., 2007c).

Pain

Pain is a common problem for patients with advanced renal disease. In a Canadian study, 50% of all haemodialysis patients reported chronic pain, and over half of these described their pain as severe (Davison, 2007). An Italian study reported a similar proportion (48%) of dialysis patients affected by pain (Mercadante et al., 2005), as did a US study which identified 50% of haemodialysis patients as reporting bone or joint pain (Weisbord et al., 2005). This is less than that reported in a more recent review synthesizing evidence across studies, which reported weighted mean prevalence for pain of 63-66% (Almutary et al., 2013). Pain prevalence in conservatively managed stage 5 CKD is similar, with baseline pain prevalence of 53% (Murtagh et al., 2007c), increasing markedly over time to affect 73% of patients by the month before death, with over half of these reporting severe pain (Murtagh et al., 2010). For those withdrawing from dialysis, pain affects about 50% of patients (Cohen et al., 2000) (Chater et al., 2006).

Pruritus

Numerous studies provide evidence on the prevalence of itch, suggesting that pruritus affects between 28% and 60% of patients on haemodialysis, and between 50% and 68% of those on peritoneal dialysis (Murtagh et al., 2007b) or, more generally, between 33-78% of those on dialysis (Almutary et al., 2013). Pruritus prevalence in those with stage 5 CKD managed without dialysis is also high (74%), suggesting it is similarly prevalent in those with ESKD not on dialysis (Murtagh et al., 2007c).

Restless legs

The reported prevalence of the symptom of restless legs among dialysis patients varies considerably, from 12% to 58% (Murtagh et al., 2007b) or 26 to 40% (Almutary et al., 2013). This compares with prevalence of at least 10–15% in the general population (Medcalf and Bhatia, 2006). For this symptom, perhaps more than any other, reported prevalence depends heavily on the definition used. Earlier studies have tended to use less well defined criteria, while more recent studies have used the specific criteria developed by the International Restless Legs Syndrome Study Group (IRLSSG) to define restless legs syndrome (RLS) (Allen et al., 2003). Of those with stage 5 disease not receiving dialysis, 48% report the symptom of restless legs (Murtagh et al., 2007c), although this study did not formal IRLSSG criteria. As with pruritus, there is some indication that RLS is associated with poorer prognosis which may again be mediated partly through impaired quality of sleep (Hui et al., 2000).

Sleep disturbance

Sleep disturbance is a common problem in patients with ESKD but it is hard to determine the exact prevalence of this problem because of the challenges of definition. Insomnia affects at least 10–15% of the general population (Drake et al., 2003), but the prevalence of sleep disturbance in renal patients is notably higher. Several studies have described prevalence and findings range from 20% to 83% (Murtagh et al., 2007b) or, in the more recent Australian review, 44-50% (Almutary et al., 2013). This wide range reflects varying definitions, but whatever definition is used, it is clear that this is a symptom which troubles many dialysis patients. Those stage 5 CKD patients who opt not to have dialysis and are managed conservatively also have a high prevalence of sleep disturbance, with 41% experiencing some difficulty with sleep, and 21% (of all conservatively managed patients) reporting severely distressing sleep disturbance (Murtagh et al., 2007c).

Fatigue

Tiredness or fatigue is also a symptom which is difficult to define, and therefore to quantify. Despite this, there is evidence that it is one of the most common symptoms experienced by renal patients; in most studies, between 70% and 97% of dialysis patients are affected by fatigue (Murtagh et al., 2007b) (Almutary et al., 2013). A very high proportion of conservatively managed stage 5 CKD patients are also affected by fatigue, with 90% of patients affected by fatigue, and 35% of all patients severely distressed by this (Murtagh et al., 2007c). Qualitative studies also suggest it is one of the most difficult symptoms for patients to cope with (Chang et al., 2001) (Murtagh et al., 2007c).

Other symptoms

Other key symptoms have been shown to be important for patients with ESKD. These symptoms include nausea and vomiting, drowsiness, breathlessness, leg oedema, dry mouth, lack of appetite and altered taste, poor concentration, dry skin, and constipation. Some symptoms, for example, breathlessness, are frequently linked to co-morbidity, such as coexisting cardiac or respiratory disease, and their prevalence very much reflects the demographics of the population, with older populations and those conservatively managed (without dialysis)—who are almost always older patients—displaying a notably higher prevalence of these symptoms (Murtagh et al., 2007c).

Symptoms due to co-morbid conditions

In those with ESKD, it is not always clear whether uraemia, dialysis, or co-morbid conditions are the most dominant cause of each symptom, and for many patients a combination of causes and triggers contributes to their overall symptom burden. Co-morbid conditions do play a major part in causing symptoms, particularly for the older patient, who may have vascular disease, cardiac problems, diabetes mellitus, or other co-morbidities. Some of the commoner co-morbid conditions which contribute to symptom burden include diabetic gastroparesis, other diabetic neuropathies, other diabetic complications, cardiovascular disease, and peripheral vascular disease.

Diabetic patients with end-stage renal disease have often had their diabetes for many years, and may have other complications in addition to their renal impairment. Diabetic gastroparesis due to autonomic nerve damage is common in long-standing diabetes, and is characterized by anorexia, early satiety (feeling full), nausea, and sometimes vomiting. Advanced uraemia itself also leads to delayed gastric emptying, which can contribute to this problem. Delayed gastric emptying may itself cause gastric reflux and dyspepsia. Diabetic patients also suffer from other neuropathies, such as autonomic neuropathies affecting the mid and lower gut, and characterized by alternating diarrhoea and constipation. Non-autonomic diabetic neuropathies that affect the peripheral nerves may occur. The neuropathic pain associated with diabetic neuropathies can be severe, persistent, and difficult to control. Skin and soft tissue problems are also common in the diabetic patient; decubitus ulcers or diabetic foot may occur and amputation may sometimes be required. The severity of these skin and soft tissue problems may be such that these pains are sometimes difficult to control.

Assessment of symptoms

Global symptom measures

Several global symptom measures have been used to evaluate the whole range of symptoms in renal disease. These include instruments used in other advanced diseases, such as the Edmonton Symptom Assessment System (Parfrey et al., 1989) (Davison et al., 2006a) (Davison et al., 2006b), and the Memorial Symptom Assessment Scale short form (Weisbord et al., 2003) (Murtagh et al., 2007c). Other measures have been validated specifically for use in those with renal disease. These include the Dialysis Symptom Index, developed from the Memorial Symptom Assessment Scale by

Weisbord et al. (Weisbord et al., 2004), and the renal version of the Patient Outcome Scale (symptom module) (Murphy et al., 2009). More comprehensive is the IPOS-Renal (Integrated Patient Outcome Scale – Renal version) which has recently been validated (Raj et al., 2018). This is a patient-centered measure of 'global' domains; that is it includes physical and psychological symptoms but also other main concerns reported by patients in advanced disease, such as information, family support, and practical matters. It is derived from the generic version of the Patient (or Palliative) Outcome Scale which is used across a wide number of conditions and countries (see www.pos-pal.org where IPOS-Renal is freely available for use).

Symptom-specific measures

Although the whole range of symptoms which patients experience needs to be assessed, there is a wider range of instruments which have been used to assess individual symptoms, such as pain, pruritus, or depression. These may provide a more detailed and accurate picture of each symptom, especially for research purposes. A range of measures are available for measurement of pain (Melzack, 1975) (Daut et al., 1983), depression (Beck and Steer, 1984) (Kutner et al., 1985) (Martin and Thompson, 2000), pruritus (Majeski et al., 2007), or RLS (Allen et al., 2009). The Cambridge–Hopkins restless legs questionnaire is based on the IRLSSG criteria, but also distinguishes RLS from other conditions, with good sensitivity and specificity (Allen et al., 2009). A range of other measures for individual symptoms exist, and are useful for research purposes, but fairly brief validated measures which capture the whole range of symptoms may be most useful in the clinical setting.

Management of symptoms

Once symptoms have been identified and assessed, they need to be actively managed. Evidence shows that management of symptoms is often suboptimal for renal patients (Davison, 2003) (Bailie et al., 2004). Renal impairment places a major constraint on use of medication, since many medicines are renally excreted, and may therefore accumulate substantially in renal impairment. For those on dialysis, careful consideration also needs to be given to the effect of dialysis on drug clearance.

Management of pain

As with any other disease group, the suspected causes of pain need to be carefully delineated, and management tailored to these causes. Pham et al provide a useful overview of the pharmacologic management of the different neuropathic and non-neuropathic pain syndromes, including examples of the typical presentations (Pham et al., 2017). Removal or specific treatment of the underlying cause when feasible is always the best approach, and only when this cannot be achieved should palliation be the main focus. Non-opioid, opioid, and adjuvant analgesics can be used in the ESKD population, but careful consideration needs to be given to:

potential risk of adverse effects, which may be exacerbated by uraemia

whether there is risk of nephrotoxicity (it is critically important not to risk remaining renal function)

elimination of the drugs used, and how this will be influenced by the renal impairment.

World Health Organization step 2 and step 3 opioids will be briefly considered here, but the reader is referred to extensive reviews of analgesic use for more details (Davies et al., 1996) (Dean, 2004) (Mercadante and Arcuri, 2004) (Murtagh et al., 2007d) (Pham et al., 2017).

Codeine and dihydrocodeine

There are reports of serious side effects following codeine use in patients with advanced renal failure, in particular profound hypo-tension (Parke et al., 1992), respiratory arrest (Talbott et al., 1997), and profound narcolepsy (Matzke et al., 1986). Dihydrocodeine is thought to have similar metabolism and elimination to codeine, and there are similar reports of prolonged narcosis (Barnes and Goodwin, 1983) (Redfern, 1983). For these reasons, use of codeine and dihydrocodeine is not recommended in ESKD.

Tramadol

Ninety per cent of tramadol is excreted via the kidneys (Lee et al., 1993), and in renal impairment, there is about a twofold increase in the elimination half-life (Lee et al., 1993). Because of this increased elimination half-life, it is recommended that the dose interval be increased to 12-hourly, and the dose reduced. Uraemia also lowers the seizure threshold, and tramadol may be more epileptogenic in ESKD patients (Gardner et al., 2000). For these reasons, an alternative drug is preferred for ESKD patients, and if the use of tramadol is absolutely unavoidable, a dose of 50 mg 12-hourly should not be exceeded.

Morphine and diamorphine

Morphine and diamorphine are not recommended for use in ESKD, because of the problems with metabolite accumulation, and because at least some of these metabolites are clinically active.

Fentanyl

Less than 10% of fentanyl is excreted unchanged in the urine. In renal failure, no dose modification appears necessary when fentanyl is given as a bolus injection (Coral et al., 1980), but there is limited evidence on the pharmacokinetics when it is administered either in repeated doses or by continuous infusion. One study suggests that the parent compound may accumulate with sustained administration (Koehntop and Rodman, 1997), and a further study demonstrates reduced clearance of fentanyl in patients with renal failure (Scholz et al., 1996). Despite these concerns about accumulation, fentanyl is, on present limited evidence, one of the preferred opioids in ESKD, because the metabolites are inactive. Some authorities suggest dose reduction with declining renal function: 75% of normal dose if creatinine clearance is 10–50 mL/minute, and 50% normal dose if creatinine clearance is less than 10mL/min (Broadbent et al., 2003). Careful monitoring for any gradual development of accumulation and toxicity would certainly be wise in any case of sustained administration (beyond 1 or 2 days), and there may be some basis for gradual dose reduction if fentanyl is used over days or weeks. Transdermal patches can be used, but careful review, with vigilance for accumulation, is important. The very wide individual variations in its pharmacokinetics (Bentley et al., 1982) (Labroo et al., 1997) would also support a cautious approach.

Alfentanil

Alfentanil is shorter acting than fentanyl, and is both less potent and less lipid soluble. Like fentanyl, it is highly protein bound and its protein binding is reduced by a high urea, but despite this the volume of distribution and elimination half-life appears unchanged in patients with renal failure (Chauvin et al., 1987). Alfentanil is therefore also one of the preferred opioids for use in ESKD, but is limited to end-of-life use, given that it is only available for parenteral use.

Buprenorphine

Buprenorphine is metabolized in the liver to norbuprenorphine, and buprenorphine-3-glucuronide, and these metabolites are principally excreted via the biliary system (Mercadante and Arcuri, 2004).

Because of its high systemic clearance and largely hepatic metabolism, buprenorphine has the potential to be reasonably safe in patients with renal failure. Some evidence shows no change in the pharmacokinetics of buprenorphine in renal impairment (Summerfield et al., 1985), but other work shows some accumulation of metabolites (Hand et al., 1990). No adverse effects were reported, and specifically no sedation or respiratory depression. Buprenorphine also has the advantage of being available in sublingual, transdermal, and injectable preparations. Note that buprenorphine is omitted from some of the reviews of analgesia in renal impairment because it is not available in all countries.

Hydromorphone

A single-dose study indicates hydromorphone accumulation in renal impairment (Durnin et al., 2001) (with proportionately greater accumulation in severe renal impairment), and a further detailed pharmacokinetic case study over 14 days (Babul et al., 1995) demonstrated clear accumulation of H-3-G. Since H-3-G is known to be a more potent neuro-excitant, there has been considerable concern about the use of hydromorphone in severe renal impairment. However, a retrospective review by Lee and colleagues (Lee et al., 2001) suggests that hydromorphone may be reasonably better tolerated than morphine in patients with renal impairment, although levels of renal impairment were small. Overall, the evidence to support the safety of hydromorphone in renal impairment is extremely limited. It may be reasonable, given the available evidence, to use hydromorphone carefully in mild or even moderate renal impairment, provided doses are reduced and the dose interval increased, and with careful monitoring and titration. In severe renal impairment, its use cannot be recommended however, until there is more evidence available.

Methadone

Methadone is metabolized mostly in the liver, and excreted both renally and faecally (Davies et al., 1996). There is large inter-individual variation, but also considerable difference between acute and chronic phase dosing (Rostami-Hodjegan et al., 1999). Some evidence suggests that plasma concentrations are no higher than in those with normal renal function (Kreek et al., 1980), suggesting that faecal excretion might compensate in those with renal impairment. Because of this, and the limited possibilities for use of other opioids, methadone has been used reasonably often for patients with renal failure and no adverse effects have been reported. Caution should be exercised on two counts, however: firstly, because of a well-described risk of accumulation and toxicity, experienced specialist supervision of methadone use should be available, and secondly, because of the wide individual variation, doses and effects should be closely monitored. The titration and use of methadone is fully described elsewhere (Morley, 1998) (Blackburn et al., 2002), but in severe renal impairment a dose reduction of 50–75% is recommended (Broadbent et al., 2003).

Oxycodone

A study by Kirvela et al. showed that the elimination of oxycodone in renal failure is significantly prolonged, and excretion of its metabolites is severely impaired (Kirvela et al., 1996), with wide inter-individual variation. Work by Kalso and colleagues also suggests that some of the effects of oxycodone may be mediated through its metabolites (Kalso et al., 1990). There are also reports of central nervous system toxicity and sedation with oxycodone in renal failure (Fitzgerald, 1991). This raises queries about the use of oxycodone in renal impairment, and there is insufficient evidence to determine whether or not it is safe to use in ESKD patients. Some clinicians use it with caution, reducing the dose and increasing the dose interval, while others avoid using it. Broadbent suggests the use of 75% of normal dose when creatinine clearance is 10–50 mL/minute, and 50% when

creatinine clearance is less than 10 mL/minute (with unchanged dose intervals) (Broadbent et al., 2003).

Management of fatigue

Fatigue is multidimensional (Lee et al., 2007), with physical, cognitive, and emotional elements (O'Sullivan and McCarthy, 2007). There is a complex but poorly understood relationship between fatigue, sleep disturbance, physical functioning, and depression in those with renal disease (Brunier and Graydon, 1992) (McCann and Boore, 2000). It is not clear, for instance, whether the reduced physical functioning which occurs with renal disease itself causes fatigue, or whether in fact the symptom of fatigue is a consequence of poor function. Fatigue is an important symptom because it is very common, highly distressing to patients, and there are a number of causes which are potentially treatable. These causes can be classified as related to the renal disease, to dialysis itself, or related to co-morbid conditions. The renal disease may cause anaemia, hyperparathyroidism, and uraemia, all of which may directly contribute to fatigue. Secondary to these direct effects are dietary and fluid restrictions, impaired nutrition, and the side effects of medications, all of which may contribute to fatigue, even if they are not the predominant causes of it. For those on dialysis, dialysis inadequacy, post dialysis fatigue, and the burden of dialysis itself may also play a part in instigating or perpetuating fatigue. Conditions unrelated to renal disease, such as hypothyroidism, should be considered and excluded. Non pharmacological managements of fatigue, such as exercise, cognitive and psychological approaches, and complementary treatments, are important, especially as pharmacological interventions become increasingly limited.

A systematic review of the use of erythropoietin-stimulating agents demonstrates that in renal patients there is a consistent relationship between haematocrit and energy/fatigue domains in quality of life (Ross et al., 2003); as haematocrit increases, so energy levels increase and fatigue reduces. When anaemia is due to kidney disease, which is likely if GFR is less than 30mL/min/1.73m2 (less than 45 in diabetics) and no other cause (such as blood loss, folic acid or vitamin B12 deficiency) is identified, then active treatment with erythropoietin-stimulating agents is likely to improve fatigue. It is not clear, however, how long treatment should be maintained in those who are nearing the end of life; most clinicians continue treatment while the patient still continues to gain symptomatic benefit.

Recently, there has been much more attention paid to exercise and rehabilitation interventions (Zhao et al., 2019). In ESKD, there is evidence that exercise can improve fatigue, anxiety, depression, physical activity, and overall quality of life; of these, perhaps fatigue and psychological wellbeing are most readily impacted; however, the optimal nature and timing of exercise interventions

Management of nausea and vomiting

Nausea and vomiting are extremely unpleasant symptoms, and are often multifactorial. Assessment requires a thorough history including establishing the history and pattern of both nausea and vomiting separately. Profound nausea and/or repeated vomiting will prevent absorption of any medications taken orally, and alternative routes (such as sublingual, rectal, or subcutaneous routes) need to be considered, at least until nausea and vomiting is controlled.

The first step is to identify the specific cause of nausea and vomiting where possible, since cause-directed treatment is most likely to succeed. Uraemia and a variety of drugs (including opioids, anticonvulsants, antibiotics, and antidepressants) can cause this kind of persistent nausea. Gastroparesis or delayed gastric emptying, (which may be caused by drugs, such as opioids, or by primary diseases, such as diabetes mellitus), usually presents with a history of post-prandial nausea

or vomiting of undigested food which relieves nausea. Bloating, epigastric fullness, flatulence, hiccough, or heartburn may accompany this. Nausea related to gastritis is often associated with heartburn, dyspepsia, or epigastric pain. Constipation may exacerbate nausea and vomiting.

For delayed gastric emptying or gastroparesis, metoclopramide can be use, although doses should be reduced by 50%, and there is an increased risk of dystonia. Haloperidol or levomepromazine is often used for nausea related to uraemia or drug-related nausea, although there is increased cerebral sensitivity, and both drugs need dose reduction. 5-hydroxytryptamine (serotonin) type 3 (5-HT3) antagonists can also be used, although the side effect of constipation will need active management. Because gastritis is common among uraemic patients, there should also be a low threshold for treatment with a proton pump inhibitor if gastritis could be a contributory factor.

Management of pruritus

The aetiology and pathogenesis of pruritus in ESKD remain unclear, and treatment options are limited in their effectiveness. Pruritus is thought to arise in C fibres located in the skin, distinct from those which mediate pain (Schmelz et al., 1997). These C fibres transmit via the contralateral spinothalamic tract to the brain (thalamus and hypothalamus) via the reticular formation (Lugon, 2005). Connections to distinct cortical areas (the anterior cingulate process, supplementary motor area, and inferior parietal lobe) then mediate, via motor areas, the powerful, almost involuntary, desire to scratch. The difficulty is that pruritus could originate at any level in this pathway (in the skin at the level of the receptors, neuropathically in the afferent nerve pathway, neuropathically in central neural pathways, or centrally from psychogenic causes). In ESKD-related itch, complex interacting factors operate at more than one place in the pathway (Lugon, 2005) (Simonsen et al., 2017), so that it is extremely difficult to elucidate any one discrete cause for itch. Current hypotheses postulate abnormal inflammatory/immune processes, dysfunction in the opioid receptor system, and/or neuropathic processes within the nervous system itself.

Immune modulators (such as ultraviolet (UV) B light, tacrolimus, and thalidomide) have been proposed to treat itch. These all act in various ways to decrease pro-inflammatory cytokines. Others have proposed disturbance in the endogenous opioids system as a cause of itch (Yosipovitch et al., 2003) (Patel et al., 2007). Kappa (κ)-opioid receptor agonists have been shown to have anti-pruritic effects in animals, and κ-opioid receptor antagonists enhance itch in animal studies (Ikoma et al., 2006). It is for this reason that opioids such as butorphanol (which has mu (μ)-opioid antagonist and κ-opioid agonist action) (Dawn and Yosipovitch, 2006), and opioids antagonists such as naloxone and naltrexone, have been proposed to treat itch. There is also some evidence that a relatively new κ-opioid agonist (nalfurafine) may be useful (Wikstrom et al., 2005) (Simonsen et al., 2017). Evidence has emerged to support the link between itch and neuropathic processes. There are a number of features of itch which suggest a neuropathic process, and Akhyani and colleagues report association between clinical neuropathy and itch in haemodialysis patients (Akhyani et al., 2005). Neuropathic agents (lidocaine, gabapentin, and capsaicin) have been used to treat itch, with some success, and there is perhaps the most evidence in support of gabapentin (Simonsen et al., 2017). However, the neuropathic component could be a secondary, rather than primary cause of ESKD-related pruritus. The role of histamine in acute itch is long established. Acute histamine-induced itch is well described, and histamine receptors appear to sensitize at least some of the C fibres which mediate itch. What is less clear is how this acute itch response relates to the chronic itch experienced by ESKD-related pruritus. Nevertheless, antihistamines are widely used in the management of ESKD-related pruritus, with varying results. A final important factor in ESKD-related itch is xerosis, or dry skin. Xerosis may be an important factor in older people with ESKD (Keithi-Reddy et al., 2007). And although uraemia is the most likely cause of pruritus, other common causes of pruritus need to be

considered if the symptom is not resolving, such as skin disorders, skin infections such as scabies, and liver impairment.

The first step in management is to optimize renal management; high phosphate may contribute to pruritus (Lugon, 2005), and dietary advice and the use of phosphate binders should be considered to reduce phosphate levels. Hyperparathyroidism may also be a contributory factor and should be considered. Dry skin may both cause and contribute to pruritus, and so should be treated actively; liberal emollients should be used if dry skin is present. Older people living alone may find it hard to apply emollients easily; spray applications are often helpful in this instance. Preventive measures, such as nail care (keeping nails short) and keeping cool (light clothing, and tepid baths or showers), are useful concurrent measures.

The evidence as to which medications are effective for pruritus is limited, often conflicting, and no one single preparation can be recommended above others. Gabapentin has the most evidence (Simonsen et al., 2017), but should be used with caution in those with ESKD, especially those without dialysis, where any clearance will be very limited. It should be used with extreme caution in ESKD patients who are not receiving dialysis.

Choice of treatment should be influenced by the stage of disease—for instance, UV light may be practical for those who remain relatively well, while antihistamines may be more appropriate nearer end of life. Time should be taken to discuss with the patient the need to persist with any one medication, and to explain and minimize side effects where possible. A clear plan of management, and persistence in following treatment through, goes a long way to helping patients cope with the distress that this symptom can sometimes cause. The psychological and social dimensions of severe itch are considerable (Murtagh et al., 2007b), and psychological, family, and social support is an important component of management.

Management of restless legs

RLS is characterized by an urge to move the legs, uncomfortable sensations in the legs, and worsening of symptoms at rest, especially during the night. The formal IRLSSG criteria are (a) urge to move the legs, usually with unpleasant sensations in the legs, (b) worse during periods of rest or inactivity like resting or sitting, (c) partial or total relief by physical activity, and (d) worse symptoms in the evening or night rather than the day (Medcalf and Bhatia, 2006). The exact cause for restless legs is not well understood but the dopaminergic system in the central nervous system is somehow disrupted (Manenti et al., 2009). There is limited evidence in uraemic RLS that iron deficiency (O'Keeffe et al., 1993), low parathyroid hormone (Rijsman et al., 2004), hyperphosphataemia, and psychological factors (Takaki et al., 2003) may play a role. Treatment should involve correction of these factors, and reduction of potential exacerbating agents, such as caffeine, alcohol, nicotine, and certain drugs (sedative antihistamines, metoclopramide, tricyclic antidepressants, selective serotonin uptake inhibitors, lithium, and dopamine antagonists) (Manenti et al., 2009). Calcium antagonists may also exacerbate RLS (Telarovic et al., 2007).

There is very limited evidence about treatment of restless legs in CKD patients, and much of the evidence is extrapolated from patients with idiopathic restless legs (Silber et al., 2004). A recent Cochrane systematic review of interventions for RLS specifically in CKD (Sinclair, 2018) included just nine studies with 220 dialysis patients. Six different interventions were evaluated against placebo or standard treatment; aerobic resistance exercise, gabapentin, ropinirole, levodopa, iron dextran, and vitamins C and E (individually and in combination). Aerobic resistance exercise showed a significant reduction in severity of RLS compared to no exercise (or exercise with no resistance), but no

difference when compared to ropinirole. A further study reported a significant improvement with ropinirole compared to resistance exercise. Gabapentin was associated with reduced RLS severity when compared to placebo or levodopa, with significant improvement in sleep quality, latency and disturbance but it accumulates rapidly if there is no dialysis; it can be given in low dose post dialysis sessions, but should be used with extreme caution in ESKD patients who are not receiving dialysis. Levodopa showed some benefit in RLS, but rebound and augmentation plus high prevalence of adverse effects were noted. Vitamins C, E and C plus E helped the symptoms of RLS with minimal side effects but were only assessed in one study. There were no studies performed in non-dialysis ESKD or peritoneal dialysis (Sinclair, 2018).

Management of sleep disturbance

A detailed history of any sleep disturbance is important, in order to identify sleep apnoea, RLS, and pruritus, which may be the underlying reason for the sleep disturbance; these each need treating in their own right initially to resolve any sleep problems. General sleep hygiene measures are important in addressing sleep disturbance; avoiding caffeine after lunch, reducing overall caffeine intake, avoiding alcohol (which is both depressant and stimulant), and avoiding daytime sleeping. If sleep apnoea is excluded, other exacerbating symptoms are treated optimally, and general measures are unsuccessful, then hypnotics may be necessary, ideally short term to attempt to re-establish sleep patterns. For those with a longer prognosis, hypnotics carry a risk of dependence, and this needs consideration in management. The shorter-acting hypnotics, such as zolpidem 5–10 mg or temazepam 7.5–10 mg, are preferable. These are generally safe in dialysis patients, although ESKD patients may be more sensitive to benzodiazepines in general, and lower doses are often required than in the general population.

Management of breathlessness towards end of life

The most common causes of breathlessness or dyspnoea in the renal patient are anaemia, pulmonary oedema (related to fluid overload or to coexisting cardiovascular disease), or co-morbidity (cardiac or respiratory disease). Anaemia produces significant symptoms including dyspnoea, and although anaemia is likely to be due to renal failure in the CKD patient, other causes should be considered and excluded. It is important to identify the underlying cause of breathlessness, since treating the underlying cause is almost always the most appropriate and effective first line of management. If volume overload is identified as a cause or contributor, more frequent or longer dialysis, with ultrafiltration, can be helpful. If treatment of the underlying cause has been exhausted, then symptomatic measures to relieve breathlessness will be required. These include general and non-pharmacological measures, psychological support, and pharmacological measures.

General measures in advanced disease include sitting upright rather than lying (which maximizes vital capacity), using a fan or stream of cool air which can provide effective symptom relief (Booth et al., 2006), inhaled oxygen if hypoxia is confirmed or suspected (Booth et al., 2004) and a calm, settled environment. For the patient whose mobility is limited by breathlessness, physiotherapy and occupational therapy can help to maximize mobility and provide appropriate aids to improve function constrained by breathlessness. Since breathlessness is a profoundly unpleasant symptom, assessment and management of the underlying psychological state is important. Breathlessness is very commonly associated with anxiety, often in an escalating cycle (anxiety causing worsening dyspnoea, which triggers worsening anxiety, and so on). Information, education, and support of patient and family are therefore critical.

As prognosis worsens, general and non-pharmacological measures will have less to offer, and pharmacological measures directed at the symptom of breathlessness itself may be more appropriate. Untreated moderate or severe dyspnoea at the end of life is very distressing, and should be treated as actively as pain or any other distressing symptom. Breathlessness is an increasingly important and dominant symptom in renal patients towards the end of life (Murtagh et al., 2010), so it is important to try and anticipate and plan for future episodes. Not all patients will, for instance, choose to be admitted for maximal treatment with intravenous diuretics in the last days or weeks of life.

Pharmacological treatments directed specifically at breathlessness include opioids and benzodiazepines (especially if there is moderate or severe associated anxiety). Low-dose opioids are helpful in relieving breathlessness near the end of life in end-stage cardiac and respiratory disease and clinical experience suggests that this is true for renal patients too. Physicians remain concerned about the use of opioids in the context of cardiac or respiratory disease, but a recent systematic review showed no evidence of significant or clinically relevant respiratory adverse effects of opioids for chronic breathlessness (Verberkt et al., 2017). However, there are considerable constraints on the use of opioids in renal patients; the guidance as for pain management should be followed, although dose of opioids for breathlessness is likely to be notably smaller (usually half or quarter the starting dose for pain) and titration upwards is undertaken to a lesser degree. If small doses are not at least partly effective, combining an opioid such as fentanyl with low dose midazolam towards the end of life (last few days or hours) may bring relief where either alone is only partially effective. This is often a better strategy than increasing the dose, since adverse effects quickly increase as doses rise.

Benzodiazepines are useful when there is coexisting anxiety (as there often is), but again need to be used with care and in reduced doses. Shorter-acting benzodiazepines are recommended, such as lorazepam 0.5–1 mg orally or sublingually four times a day (if used sublingually, it has a quicker onset of action and may more readily restore a sense of control to the frightened and anxious patient). If the patient is in the last days of life, midazolam (at 25% of normal dose if eGFR is less than 10) can be given subcutaneously and titrated according to effect. Midazolam can be given every 2–4 hours, although ESKD patients are sensitive to its effects and do not usually need frequent or large doses. A starting dose of 1.25 or 2.5 mg is common, and often sufficient. If more than one or two doses are required, a subcutaneous infusion over 24 hours is most practical.

Communication and advance care planning

There is growing evidence on the information provided to, and the communication needs of, patients with ESKD, as well as the kind of trade-offs that patients are willing to accept. In a recent study, patients were willing to forgo 23 months of life expectancy with home-based dialysis in order to decrease their travel restrictions, although there is inconsistency between patient and family preferences (Morton et al., 2012a). Communicating early and clearly about the options and possibilities is an important part of good quality care.

The evidence also provides wider pointers for clinicians, and although it is not yet sufficient for definitive conclusions (Lim et al., 2016) some lessons are clear. First, detailed discussions about the future and about preferences and priorities do not remove hope, as some professionals believe; rather, they sustain realistic hope and empower patients to work towards possibilities consistent with their own values (Davison and Simpson, 2006). Second, there are a variety of reasons why patients opt for conservative management (Noble et al., 2009) (Bristowe et al., 2019). These will influence how patients and families view the future, after the decision is made; a patient who views

conservative management as a 'logical and affirming choice' will respond differently to one who is 'angry and believed they were somehow giving up on life' (Noble et al., 2009). Subsequent advance care planning therefore needs to be responsive to the perspective patient and family bring to the process; it is about helping them towards greater empowerment, whatever the starting place, but some will have a very different psychological journey ahead, as compared with others. Third, advance care planning is not only about key medical decisions, such as decisions about dialysis, or agreement to 'not for resuscitation' order when in hospital. When done well, it also involves enhancement of the final days, weeks and months with positive decisions about family relationships, resolution of conflict, and living well until the end of life (Hines et al., 2001); all priorities which patients themselves rate highly (Singer et al., 1998). This approach helps move away from isolated decisions about the utilization of medical supportive measures, which are sometimes influenced more by transient factors than by stable 'core' values (Fried et al., 2007), and builds on a more integrated person- and family-centred care.

There is some overlap between making dialysis decisions and planning ahead for subsequent care, because the former will inevitably involve some exploration of the patient's preferences and priorities. However, advance care planning becomes more far-reaching as the illness progresses. Patients and families often want advice and information, such as what to expect at different stages, when and why hospitalization might be appropriate, what other active management is right for them, who is available to care for them at home, and where do they prefer to be cared for and to die, if practicable. This is a dynamic and evolving process, not one or even a few fixed episodes, and there needs to be good liaison to ensure it is effective. Timing is critical; not all issues will be right to discuss at any one time, and there will need to be evolution in discussions as the disease itself advances. There is a fine balance between introducing issues for discussion too early, and leaving them too late, so that opportunities are missed, and 'default' care becomes inevitable (Holley, 2003). A realist review of interventions to support ACP in kidney disease identified two main components which improve results: training for health care professionals that addresses concerns, optimizes skills, and clarifies processes and use of clear and simple documentation and processes that are individually tailored, culturally appropriate, and involve family (O'Halloran et al., 2018). Communication among professionals is critical; there may be a number of professionals who also need to be aware of decisions, preferences, and priorities, including primary care professionals, who may have major responsibility if the patient is at home.

There has been some study of the experience of illness among conservatively managed stage 5 CKD patients (Selman et al., 2019), and this work suggests that loss of control and related uncertainty are a particular feature for these patients. Advance care planning can help reduce this sense of loss of control (Davison and Torgunrud, 2007). This is important, since for a number of these patients, the prospect of death was not their main concern; uncertainty about the path of their illness before death troubled them more. Above all, participants expressed a wish not to be a burden to their family and others (Murtagh, 2009); advance care planning helps to make explicit preferences and priorities about care, and identifies what can be provided to support families and reduce that burden (provided, of course, that appropriate services are available).

Conclusions

People with ESKD have extensive palliative care needs. They therefore need significant medical, nursing, psychological, and social care as their illness advances towards the end of life. This chapter has focused on the challenges of symptom recognition, assessment, and management, and the need for advance care planning, but has not addressed the considerable psychological, spiritual, and

practical care that these patients need, or the high level of coordination between providers that is important for ensuring effective and accessible care.

Symptoms can arise directly from the renal disease itself, as a consequence of dialysis, or from co-morbid conditions (particularly in older patients). This diversity makes them harder to assess and address, and detailed assessments and interventions are needed. Pharmacological management of symptoms is one of the most challenging aspects of the care of those with ESKD. Although the emphasis in this chapter has been on pharmacological management, it should be stressed that psychological, social, and spiritual aspects of management are also important, especially towards the end of life. It is for this reason that care of renal patients is best managed with multi-professional teams, including counsellors and psychologists, occupational therapists and physiotherapists, dieticians, and chaplains, and most importantly, professionals with both nephrology and palliative care skills.

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