

Palliative care for patients with advanced chronic kidney disease

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ABSTRACT Over the past three decades there has been a dramatic rise in the number of patients with advanced chronic kidney disease. The fastest expanding group receiving dialysis has been the elderly. However, for those patients who are very elderly with co-morbidity, dialysis may not offer a survival advantage. Therefore, active conservative management is a growing service offered by many renal units in the UK and focuses on non-dialytic correction of fluid and electrolytes, management of renal anaemia, and assessment and management of symptoms.

The five-year survival of a patient over 75 years of age starting dialysis is 20% and if a patient is over 75 years, has co-morbidity, or a poor performance status, dialysis may not offer any survival advantage. Whether a patient is managed by dialysis or by conservative management the symptom burden suffered is high. These symptoms are under-recognised and often managed poorly because of increased drug toxicity in renal failure. This complex group of patients require close working between renal, palliative care, medicine for the elderly, and community teams, to allow best quality of life and end of life care. This review describes some of the challenges in providing Advanced Care Planning for dialysis and conservatively managed patients, highlights the symptom burden of patients with advanced chronic kidney disease, and offers guidance in how to manage the symptoms effectively.

KEYWORDS chronic kidney disease, dialysis, opioids, pain, palliative care.

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OVERVIEW

Prevalence of renal failure

In recent years there has been a dramatic increase in the number of patients receiving renal replacement therapy, to 110 patients per million population. This has been in association with a rise in the prevalence of diabetes and hypertension in an ageing population, coupled with the automatic reporting of estimated glomerular filtration rate (eGFR). The fastest expanding group receiving dialysis has been the elderly.

Survival, disease trajectories, and advanced care planning

Forty per cent of patients will receive a kidney transplant and may live a long life. However, over half of patients with advanced chronic kidney disease (CKD) remain on long-term dialysis and have a significantly reduced life expectancy without realistic prospect of transplant. Several theoretical models have been put forward to describe the physical trajectories to death (see Figure 1). There is limited evidence on the disease trajectory in renal disease. However, it is clear that there is not one

trajectory that fits all patients with advanced CKD. The option of dialysis makes the trajectory more complex and unique from other organ failures.

Survival and dying trajectory on dialysis

The median age of patients starting dialysis is 65 years. The expected remaining life years of someone receiving dialysis in the age group 65–69 years is only 3.9 years, compared with 17.2 years for an age-matched population. The limited available evidence indicates that in patients over 75 years with significant co-morbidity and/or poor functional status (WHO Performance Status 3) dialysis does not offer a survival advantage.

Sudden death

Patients on dialysis may have a sudden, unpredictable death, often due to cardiac disease (Figure 1A).

Terminal illness

Due to a change in the clinical condition, the patient and renal team may decide that dialysis withdrawal is the best option; the median life expectancy if there is no residual renal function is then 8–10 days. However this may be prolonged to a few weeks if the patient is passing

urine and/or has underlying residual renal function. In most cases after dialysis withdrawal, death can be predicted with relative certainty (Figure 1B).

Organ failure

Often patients initially do well on dialysis but at some point start to decline and recurrent hospital admissions may be required for sepsis, difficulty with vascular access, and other co-morbidities. Recovery may occur but overall functional status continues to decline. Predicting and planning for the dying phase can be difficult if the general decline is not recognised (Figure 1C).

Survival of conservatively managed patients

Conservative management is becoming an established treatment option in many renal units. Although the numbers are not collected by the UK Renal Registry studies suggest that approximately 15–20% of patients with advanced CKD who are receiving nephrology care are managed conservatively.

Frailty

Many CKD patients are elderly with poor functional status and multiple co-morbidities. They may decline gradually over time, requiring an increase in medical and supportive services. Life expectancy for this group of patients may range from a short number of months to approximately two years. Those patients with a rapid loss of renal function and/or other co-morbidities have a poorer prognosis. The emphasis is on slowing the decline in kidney function (by measures such as good blood pressure management), non-dialytic correction of electrolyte and fluid imbalances, management of anaemia, and assessing and managing symptoms. As patients become frailer they may no longer be able to travel to a renal clinic and services should be flexible to allow palliative and supportive care to continue in the community (Figure 1D).

Advanced Care Planning

The trajectory to death is variable in renal patients depending on the treatment option, age, functional status and co-morbidity of the patient.

Ideally, Advanced Care Planning should start when patients reach end-stage renal failure and are being informed about treatment options. This means that pre-dialysis education has to be tailored to the individual, taking into account their age, functional status, and co-morbidities.

Evidence shows that renal patients want to talk about end of life and prognosis and honest information should be given about what dialysis can offer frail elderly patients. For those who initially start dialysis and then subsequently deteriorate, access to the same level of Advanced Care Planning, symptom control and

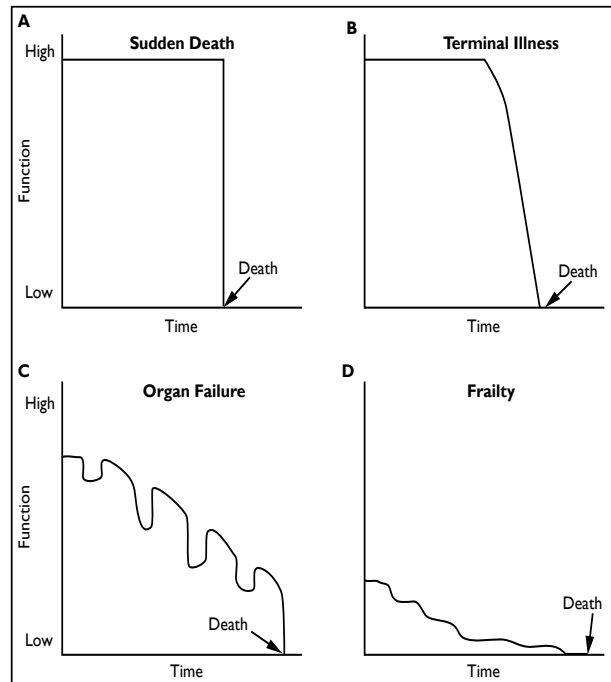


FIGURE 1 Typical disease trajectories identified in patients with different diseases (From: Murray SA et al. *Illness trajectories and palliative care. BMJ* 2005; 330: 1007–11)

supportive services as may be offered to those patients managed conservatively should occur. This requires joint working between renal teams, palliative care teams, medicine for the elderly and primary care teams.

Although prognostication can be very difficult, tools such as the Gold Standards Framework or the Supportive and Palliative Care Indicators Tools are useful to help identify those patients who are at risk of deteriorating and dying. They allow the focus of care to concentrate on improvement of symptoms and quality of life in the last 12 months of life, as well as optimal management of the underlying condition if appropriate.

At a minimum, ‘the surprise question’ – ‘Would you be surprised if your patient died in the next 6–12 months?’ – should be used to identify those patients who may benefit from increased palliative and supportive care.

Symptom burden and symptom management in advanced CKD

It is now recognised that many patients with renal failure, whether they are managed conservatively or by dialysis, have a high symptom burden. The symptom burden is comparable to patients with terminal cancer or end-stage cardiac failure (Figure 2). Whilst dialysis can relieve some symptoms it can also add to symptoms. It is also important to recognise the total symptom burden that patients experience. Pain, for example, may be more burdensome if the patient is also experiencing

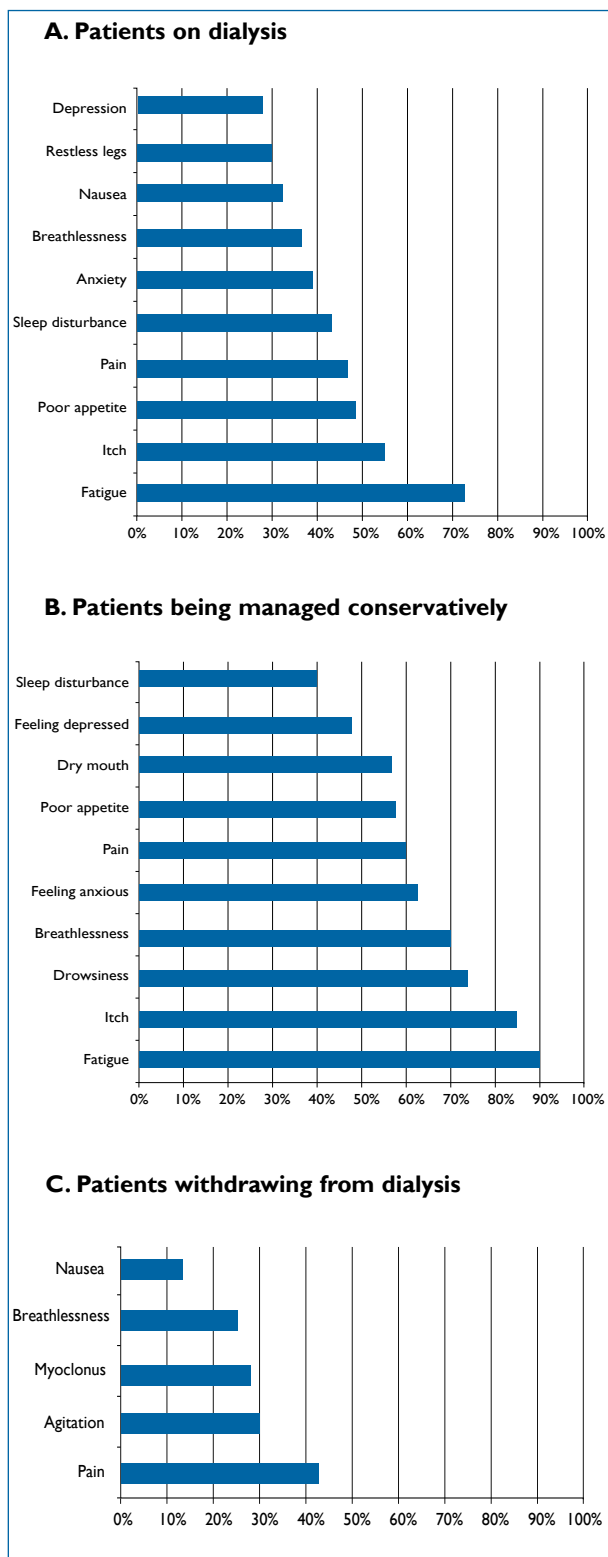


FIGURE 2A–C Percentage of patients with common symptoms in renal disease

restless legs, nausea, and low mood, simultaneously. The common belief is that a uraemic death is relatively symptom free. However, the evidence suggests that a significant minority of people continue to experience distressing symptoms in the dying phase.

Symptom assessment

Identifying and managing symptoms in renal patients is important. However, evidence shows that symptoms in renal disease are infrequently assessed and often under-recognised. Ideally symptoms should be routinely assessed without waiting for patients to raise them. Valid tools to capture symptom scores in renal patients include:

- renal version of the patient outcome scale – symptom module 2
- modified Edmonton symptom assessment scale 4

Symptom management

In patients whose eGFR < 30 mL/min (CKD stage 4 and 5) drug toxicity is common. Many of the drugs that are normally used for symptom control will lead to toxicity in patients with renal failure. In general it is often necessary to both reduce the dose of a drug and increase the dosing interval. It may be important to avoid specific drugs if they are nephrotoxic, are excreted by the kidneys, or have active metabolites that are excreted by the kidneys. This requires careful choice of medication and monitoring for toxicity as well as for improvement in symptoms. It is best to use short-acting preparations and avoid the use of sustained-release preparations.

Evidence is limited, therefore the following guidance is based on Level 3 and 4 evidence.

Drugs and dialysis

For those patients receiving dialysis, the effects of dialysis on the drug should be considered as removal of the drug will depend on its molecular size, water solubility, protein binding, and dialysis-related factors. An up-to-date review of the effects of dialysis on drugs should be used for guidance (e.g. Dialysis of Drugs 2013).

PAIN IN ADVANCED CKD

Moderate to severe pain is common and multifactorial in patients with renal failure (see Box 1).

BOX 1 CAUSES OF PAIN

1. Renal-specific pain – polycystic kidneys, amyloid, calciphylaxis (complex pain caused by tissue ischaemia due to calcification of small vessels/subcutaneous tissue).
2. Dialysis-specific pain – Steel syndrome (vascular insufficiency associated with an AV fistula), headache, fistula problems, abdominal pains from peritoneal dialysis.
3. Musculoskeletal pains – renal osteodystrophy, osteomyelitis, muscle spasms, cramps, restless leg syndrome, osteoporosis, carpal tunnel syndrome.
4. Neuropathic pain – renal or diabetic neuropathy.
5. Ischaemic pain – peripheral vascular disease, vasculitis.

MANAGEMENT OF PAIN

Which choice of opioid?

Most opioids are metabolised through the liver to active or inactive metabolites. The metabolites and some of the unchanged drug may be excreted by the kidneys. The opioids that are least likely to cause toxicity are metabolised and cleared at least partly through the biliary system, or have no active metabolites. With careful choice and monitoring of the patient, pain control can be achieved without toxicity. Signs of opioid toxicity include drowsiness, hallucinations, myoclonic jerks and respiratory depression.

Most pains can be treated by following an adapted WHO analgesic ladder as suggested below.

Step 1 – Paracetamol is safe to use in renal failure. NSAIDs should be avoided as they will further impair renal function and there is an increased risk of gastrointestinal bleeding due to the effects of uraemia on the platelets.

Step 2 – Weak opioids

- Codeine, dihydrocodeine and their derivatives should be avoided as these are metabolised to many active metabolites including morphine and its metabolites. Both the unchanged drug and the metabolites accumulate and there is significant

evidence of respiratory depression and drowsiness following their use, particularly with repeated dosing.

- Tramadol is metabolised to one active metabolite. Both tramadol and its metabolite accumulate in renal failure. It may be safer than codeine but can still cause respiratory depression; therefore the dose should be reduced, the dosing interval increased to twice daily, and monitoring for adverse effects should occur.

Buprenorphine now exists in a low-dose patch (BuTrans) and therefore may act at the level of a weak opioid. It is metabolised in the liver to norbuprenorphine and buprenorphine-3-glucuronide, which are less active or inactive. The metabolites are excreted via the kidneys whilst 15% of the unchanged drug is cleared through the biliary system. Pharmacokinetic studies in humans with renal failure have not found adverse effects of buprenorphine and therefore it can be cautiously recommended at low dose if patients are unable to tolerate tramadol. Specialist advice should be gained and an Individual Patient Treatment Recommendation form will need completed in Scotland as it is not Scottish Medicines Consortium approved.

Step 3 – Strong opioids

- Morphine and diamorphine are metabolised in the liver to many active metabolites including morphine-3-glucuronide and morphine-6 glucuronide. The metabolites are potent and can cause significant

TABLE 1 Opioid conversion chart (approximate). Use with caution and contact specialist palliative care if further advice required

Opioid	Dosage >				
Tramadol (oral)	50–100 mg		100–200 mg	150–300 mg	
Codeine (oral)	100 mg		200 mg		
Morphine (oral)	10 mg	15 mg	20 mg	30 mg	60 mg
Fentanyl (sublingual)		100 mcg		200 mcg	400 mcg
Buprenorphine patch (BuTrans [7 day patch])	5 mcg		10 mcg	15 mcg	30 mcg
Oxycodone (oral)	5 mg	7.5 mg	10 mg	15 mg	30 mg
Alfentanil (subcutaneous)	300 mcg	500 mcg		1 mg	2 mg
Diamorphine (subcutaneous)		5 mg		10 mg	20 mg
Fentanyl patch (transdermal)				12 mcg	12–25 mcg

Note: When switching opioids incomplete cross-tolerance occurs and there is wide inter-individual variation. Therefore best practice is to reduce the new opioid by 25-30% and gradually titrate upwards if required. Patients should be monitored closely for toxicity.

BOX 2. PROPOSED STEPWISE PLAN FOR MANAGEMENT OF PAIN IN PATIENT WITH EGFR<30 ML/MIN.

Step 1

Paracetamol 1g three times a day*

Step 2

BuTrans patch (buprenorphine) 5 µg/hr to change every 7 days (maximum 15 µg/hr)**

Or

Tramadol IR 50 mg twice daily (maximum 100 mg/24 hrs)***

If patient intolerant of step 2 analgesic due to side-effects, consider low dose step 3 opioids. If at maximum step 2 and still in pain convert to a fentanyl patch.

Step 3

Oxycodone IR 1 mg twice daily and titrate up to 5 mg three times a day in short term

Then convert to fentanyl patch 12 µg/hr to change every three days and titrate up

For breakthrough pain relief consider oxycodone IR

*Avoid codeine, morphine and diamorphine as these have metabolites which accumulate in renal failure resulting in toxicity and may result in respiratory depression.

**Buprenorphine (BuTrans) Patches are not yet approved by the Scottish Medicines Consortium. Therefore an exceptional use form must be filled in for patients.

***Do not prescribe tramadol to patients who are on SSRIs.

respiratory depression and drowsiness. Both the unchanged drug and the metabolites are excreted by the kidneys and are found to accumulate in renal failure, leading to significant toxicity. These drugs should be avoided in patients with CKD Stage 4 and 5 (eGFR < 30 ml/min).

- Oxycodone is metabolised in the liver to noroxycodone and oxymorphone which are both active, although possibly less so than the metabolites of morphine. Both oxycodone and its metabolites are cleared by the kidneys, thus accumulation can occur. Limited evidence suggests that it is less likely to cause the same degree of toxicity as morphine and diamorphine; however, it cannot be recommended. If required, the short-acting form should be used at a low dose with an increased dosing interval.
- Hydromorphone is metabolised to hydromorphone-3-glucuronide. The activity of this metabolite is unknown in humans. Both parent drug and metabolite are cleared through the kidneys. Limited evidence suggests that hydromorphone is better tolerated in renal failure than morphine but not enough evidence exists for it to be recommended.
- Fentanyl has no active metabolites but 10% of the unchanged drug is excreted by the kidneys, therefore

accumulation may occur. Fentanyl can be recommended as long as there is cautious titration of the dose and careful monitoring for toxicity.

- Alfentanil is a potent short-acting synthetic opioid which has no active metabolites and only 1% is cleared through the kidneys. Pharmacokinetic studies have found no accumulation in renal patients. It can be recommended, however, due to its very short half-life it is best used only if a continuous infusion is required. It is 30 times more potent than oral morphine, therefore advice should be sought before prescribing.

An opioid conversion chart is shown in Table 1.

Neuropathic pain

Adjunctive treatment is often effective in neuropathic pain and should be commenced early:

- Gabapentin 100 mg at night or pregabalin 25mg twice daily – accumulate in renal failure and main side-effects are drowsiness and dizziness therefore careful titration and a reduced dose is required.
- Amitryptiline 10 mg at night (maximum dose 100 mg at night) – avoid in patients with cardiac disease as risk of cardiac arrhythmias.

Box 2 illustrates how pain can be managed in a patient with CKD stage 4 or 5.

MANAGEMENT OF NAUSEA AND VOMITING

Firstly, establish the likely cause of nausea and vomiting as the different anti-emetics work on different receptors. Uraemia can cause persistent nausea and is best managed by drugs which act at the chemoreceptor trigger zone.

- Haloperidol is the drug of choice for uraemia-induced nausea. The dose of haloperidol should be reduced due to accumulation and increased cerebral sensitivity.
- Domperidone/metoclopramide if gastroparesis or delayed gastric emptying is suspected. This is common in diabetic or uraemic neuropathy. Metoclopramide accumulates and there is an increased risk of extrapyramidal reactions, therefore dose reduction is required.
- Levomepromazine if nausea and vomiting becomes refractory as it is a broad spectrum anti-emetic acting at many receptors.

MANAGEMENT OF URAEMIA-INDUCED PRURITUS

The pathogenesis of pruritus is multifactorial. Triggering factors include uraemia-related abnormalities (calcium,

phosphorus and parathyroid hormone metabolism), accumulation of uraemic toxins, systemic inflammation, cutaneous xerosis, the opioid system and the serotonergic system.

There is no strong evidence for any particular treatment, although small trials have shown limited positive effects for various treatments below.

Stepwise management of uraemia-induced pruritus

1. Aim to normalise parathyroid hormone, calcium and phosphorus levels.
2. For the dialysis patient ensure optimal dialysis.
3. Use of regular water-based skin emollients applied 2–3 times daily such as Aveeno lotion, Doublebase or Diprobase.
4. Gabapentin has some supporting evidence for pruritus although it accumulates in renal failure and may induce drowsiness. It should be given after dialysis.
5. Mirtazepine. Selective noradrenaline reuptake inhibitors relieve itch possibly by reducing central sensitisation to itch due to their effects on both serotonin and noradrenergic alpha-2 receptors.
6. Antihistamines do not reduce uraemic pruritus however a sedating antihistamine may help with sleep disturbance.
7. Phototherapy. UVB light has good supporting evidence for refractory pruritus.

RESTLESS LEGS

Restless legs syndrome is characterised by an urge to move the legs, usually with unpleasant sensations in the legs. The sensations are made worse by rest, increase at night, and are often completely relieved by physical activity. The underlying cause is not completely understood but it is believed that the dopaminergic system in the central nervous system is disrupted. There is limited evidence to suggest that iron deficiency, low parathyroid hormone, hyperphosphataemia, and psychological factors may play a role. Correction of these factors may help. Gabapentin is often effective as are the dopamine agonists pergolide and pramipexole. Clonazepam may also be useful; however, it may cause excessive drowsiness.

DYSPNOEA

- Dyspnoea in renal failure is often multifactorial (renal anaemia, pulmonary oedema, or co-morbidity). Identifying and treating the cause is often the most appropriate thing to do to improve symptoms.
- Fluid removal by dialysis, appropriate diuretic use, and fluid restriction may be required.
- Treatment of anaemia with measures such as erythropoietin and iron infusions may improve symptoms of dyspnoea and fatigue.

- Non-pharmacological measures such as use of a fan, oxygen if hypoxia is confirmed, specific exercises from physiotherapy, and aids from occupational therapy may improve function limited by dyspnoea.
- When approaching the last days of life, other measures to improve symptom control may be required with less scope for reversing the underlying problem. If anxiety is a significant component of the breathlessness, low dose, short-acting benzodiazepines may be used such as lorazepam. Midazolam becomes unbound in renal failure and may lead to excessive drowsiness, therefore reduced doses should be used. Low dose opioids can also be given to relieve breathlessness, but should be chosen carefully and monitored to avoid toxicity.

MANAGEMENT OF RESPIRATORY TRACT SECRETIONS

A patient dying with renal failure may require infusions of diuretics to reduce pulmonary oedema or haemofiltration. This would be done at the advice of the renal team. However, usually the use of anticholinergic drugs can reduce respiratory secretions and can be given in a syringe driver. Hyoscine butylbromide and glycopyrronium are both recommended although the latter may require dose reduction due to accumulation. Hyoscine hydrobromide is not recommended due to increased cerebral sensitivity.

MANAGEMENT OF ANXIETY AND AGITATION

Look for underlying cause and treat any reversible causes. If anxiety is the main component lorazepam or diazepam can be used. However, if the patient is in the last days of life and unable to swallow, midazolam can be given but in reduced doses to prevent excessive drowsiness. If delirium is the dominant symptom then low-dose haloperidol is the drug of choice.

END OF LIFE CARE

When the clinical team agree that the patient is in the last days of life then the aim of treatment is the comfort of the patient and the support of those close to them. An individualised end of life care plan should be started and anticipatory prescribing should occur for those symptoms the patient may experience. Careful choice of drug will prevent toxicity and any exacerbation of symptoms. Often a dying patient is unable to swallow and it is appropriate to administer the medication through a continuous subcutaneous infusion.

HIGHLIGHTS

- Advanced chronic kidney disease is increasing in prevalence due to the rising age of the population, the increased prevalence of diabetes and hypertension and the automatic reporting of estimated glomerular filtration rate. The elderly are the fastest expanding group receiving renal replacement therapy.
- The overall life expectancy of someone on dialysis is significantly reduced compared with age-matched populations. However, for the >75 year age group with co-morbidity, dialysis may offer no increase in longevity and conservative management should be considered.
- Advanced Care Planning can be complicated in renal patients as their disease trajectory is complex and dependent on choice of treatment modality, age, functional status, and co-morbidity, therefore planning for last months of life should be tailored to the individual.
- Total symptom burden is high in both dialysis and conservatively managed patients but is often under-reported and managed poorly. Common symptoms are pain, anxiety, dyspnoea, pruritus, anorexia, fatigue and drowsiness.
- Choice of drug is important in symptom management as drug toxicity in renal failure is common and can exacerbate symptoms. With careful use of medication many symptoms can be controlled well. Opioids such as codeine, morphine and diamorphine should be avoided and opioids that have inactive metabolites should be used such as fentanyl and alfentanil.

Further reading

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Web resources

- 1 Bailie GR, Mason NA. *2013 Dialysis of Drugs*. Michigan: Renal Pharmacy Consultants, 2013. <http://renalpharmacyconsultants.com/assets/2013dodbooklet.pdf>
- 2 Edmonton Symptom Assessment System. <http://www.palliative.org/newpc/professionals/tools/esas.html>
- 3 Advance Care Planning. <http://www.goldstandardsframework.org.uk/advance-care-planning>
- 4 The GSF Prognostic Indicator Guidance. <http://www.goldstandardsframework.org.uk/cd-content/uploads/files/General%20Files/Prognostic%20Indicator%20Guidance%20October%202011.pdf>
- 5 The Palliative Care Outcome Scale. POS – symptom module 2. <http://pos-pal.org/maix/pos-s-in-english.php>
- 6 Palliative Care Guidelines. NHS Scotland. <http://www.palliativecareguidelines.scot.nhs.uk>
- 7 Supportive and Palliative Care Indicators Tool (SPICT™). <http://www.spict.org.uk/>

SELF-ASSESSMENT QUESTIONS

1. A 79-year-old lady with advanced CKD being managed conservatively attends clinic. She has long-standing osteoarthritis which has worsened recently and has been taking two tablets of co-codamol 30/500 mg four times daily. Although the pain is controlled better she is drowsy and nauseated. Her bloods show that her renal function continues to decline and her eGFR is 11 ml/min.

Which ONE of the following is the most appropriate action?

- A. Stop the co-codamol and give the patient regular paracetamol.
- B. Stop the co-codamol and give tramadol 100 mg four times daily.
- C. Stop the co-codamol and give tramadol 100 mg bd.
- D. Stop the co-codamol and give the patient regular paracetamol and a NSAID.
- E. Continue the co-codamol and give haloperidol for the nausea.

2. An 81-year-old man with known renal impairment from hypertension and a background of ischaemic heart disease, congestive cardiac failure, and type 2 diabetes has had a gradual decline in his eGFR from 25 ml/min to 14 ml/min over the past 12 months. He is unable to get out of the house independently as is limited by dyspnoea. He and his family are very keen that he is prepared for dialysis and want as much information about prognosis as possible.

Which ONE of the following do you tell them?

- A. He should consider being managed conservatively as dialysis is unlikely to increase his survival and he will spend less time in hospital. He may be in his last 1–2 years of life.
- B. He should start dialysis as this will increase his life expectancy by up to 10 years.
- C. He should start peritoneal dialysis.
- D. He should consider starting dialysis as without it he is likely to die within the next 12–24 months.
- E. He should consider being managed conservatively as although this will shorten his length of life it is likely to keep him out of hospital, compared to being on dialysis.

3. A 71-year-old man has type 2 diabetes, peripheral vascular disease, has been failing on dialysis with poor vascular access and has recurrent sepsis from a gangrenous foot. He is not fit for amputation and it is likely that he will die within the next few weeks. He has been receiving oral morphine for the pain but this may not be absorbed as he has nausea and vomiting. He is also itchy and drowsy. You wish to improve his symptoms.

Which ONE of the following would you do?

- A. Switch the morphine to alfentanil in a syringe driver and add haloperidol to the syringe driver.
- B. Inject the morphine intramuscularly and prescribe a laxative and metoclopramide.
- C. Convert the morphine into a syringe driver and add ondansetron.
- D. Convert the morphine to a fentanyl patch and give intramuscular cyclizine.
- E. Switch the morphine to oral oxycodone and prescribe metoclopramide.

4. A 75-year-old lady with hypertension, diabetes, and CKD stage 5 from diabetic nephropathy is being managed conservatively without dialysis. She has a good performance status and is completely independent but has made this treatment choice along with the nephrology team. She develops severe pruritus. Her eGFR is 10 ml/min, calcium and phosphate are at normal levels.

Which ONE of the following is your first choice of treatment?

- A. Start mirtazepine.
- B. Start gabapentin 100 mg at night.
- C. Refer to dermatology for UVB light phototherapy.
- D. Start a non-sedating antihistamine such as cetirizine.
- E. Start twice daily application of Diprobase aqueous cream.

This paper was originally published as part of the Palliative Care module on the RCPE Online Education Portal. Specialty Modules for continuing medical education, including the answers to these questions, are available to Fellows and Members at <http://learning.rcpe.ac.uk>