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Symptom management for the adult patient dying with advanced chronic kidney disease: A review of the literature and development of evidence-based guidelines by a United Kingdom Expert Consensus Group

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Abstract: Improvement in end-of-life-care is required for patients dying with chronic kidney disease (CKD). The UK government now recommends that tools such as the Liverpool Care Pathway for the Dying Patient (LCP) be used to enhance the care of those patients dying with CKD. The LCP was originally developed for patients dying with terminal cancer, however has been shown to be transferable to patients dying with heart failure or stroke. On this background, in 2005 a UK National Renal LCP Steering Group was formed. The aim was to determine whether or not the generic LCP was transferable to patients dying with CKD. An Expert Consensus sub-group was established to produce evidence-based prescribing guidelines to allow safe and effective symptom control for patients dying with renal failure. These guidelines were finalised by the Expert Consensus group in August 2007 and endorsed by the Department of Health in March 2008. A literature search on symptom control and end-of-life care in renal failure was performed. A summary of the evidence was presented at a National Steering Group meeting. Opinions were given and provisional guidelines discussed. A first draft was produced and individually reviewed by all members of the Expert Group. Following review, amendments were made and a second draft written. This was presented to the entire National Steering Group and again individual comments were taken into consideration. A third and fourth draft were written and individually reviewed, before the guidelines were finalised by the Expert Consensus group. Patients dying with advanced CKD suffer symptoms similar to patients dying of cancer. The Renal LCP prescribing guidelines aim to control the same symptoms as the generic LCP: pain, dyspnoea, terminal restlessness and agitation, nausea and respiratory tract secretions. The evidence for the production of the guidelines is discussed and how a consensus was reached. A summary of the guidelines is given and the complete guidelines document is available via the Marie Curie Palliative Care Institute, Liverpool website. *Palliative Medicine* (2009); **23**: 103–110

Key words: kidney disease; symptoms; symptom management; guidelines; dying; opioids

Introduction

The number of patients developing chronic kidney disease (CKD) is rising. In 2004, the incidence of adults accepted for renal replacement therapy in the United Kingdom (UK) was 103 per million population.[1] This number is believed to be rising by approximately 10% annually.[2] Moreover, studies suggest that a further 20% of patients with advanced CKD are managed conservatively without dialysis.[3] Importantly, the increase in the numbers is not uniform and the proportion of older patients reaching advanced CKD is rising rapidly. Patients over 65 years who start dialysis have a 5-year median survival of 14.5%.[1] Studies suggest that for those older patients with high comorbidity dialysis may offer no survival advantage.[4,5] This specific group of patients have a poor prognosis and high symptom burden whether or not they receive dialysis. There is growing recognition from both renal and palliative professionals that improvement in end-of-life care is required for patients dying with CKD.[6–9] When Part 2 of the UK National Services Framework for Renal Disease was published in 2005, one-third of it was devoted to end-of-life care.[10] One of the quality requirements documented is that people with established renal failure near the end-of-life should have a jointly agreed palliative care plan. It suggests that tools such as the Liverpool Care Pathway for the Dying Patient (LCP) should be used to enhance the last days of life for patients dying with CKD. The LCP is an evidence-based framework, originally developed in order to transfer the quality of care given to cancer patients in the hospice setting, given to patients dying of cancer in the acute hospital setting and community.[11] It has since been shown to be transferable to

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support patients dying of end-stage heart failure and stroke.[12,13]

On this background a National Renal LCP Steering Group was formed in September 2005, under the auspices of the Marie Curie Institute Liverpool and the National Council for Palliative Care. The aim was to determine if the generic LCP framework was transferable to patients dying with advanced CKD. The Steering Group included physicians and clinical nurse specialists from Palliative Medicine and Nephrology, representatives from the Department of Health, National Kidney Federation, National Council for Palliative Care and the End of Life Programme and LCP Facilitators from within England. An Expert Consensus subgroup was established with the specific task of identifying how the generic LCP prescribing guidelines needed to be adapted to allow safe symptom control at the end-of-life in a patient dying with advanced CKD.

The Expert Consensus group consisted of four consultants in Palliative Medicine, two consultants in Nephrology, one specialist registrar in Palliative Medicine and one research training fellow in Palliative Medicine. All members had interest and clinical experience in renal palliative care.

The remainder of this article will describe the work of the Expert Consensus group and the production of evidence-based prescribing guidelines for symptom control in the last days of life for a patient dying with advanced CKD.

Methods

A literature search was performed by the authors using three electronic databases accessed from the OVID search engine: MEDLINE (1966 to May 2006), EMBASE (1980–2006) and CINAHL (1982–2006). To complement this, textbooks of renal medicine and palliative medicine were explored for relevant articles.[14–16] Reference lists of included articles and papers were also searched. Keywords and medical subject headings were grouped into three broad areas for the search to capture the relevant literature on symptom management at the end-of-life in CKD. The three areas were renal failure, symptoms and management. For renal failure, search terms included CKD, advanced kidney disease, end-stage renal disease (ESRD) and dialysis. For symptoms, search terms included end-of-life, nausea, vomiting, pain, dyspnoea, respiratory tract secretions, anxiety and agitation. Search terms for management included symptom control, opioids, analgesics, antiemetics, glycopyrronium, benzodiazepines, hyoscine butylbromide and hyoscine hydrobromide.

Terms within each group were combined using the Boolean operator 'OR', and each group was then combined using 'AND'.

All titles and abstracts were reviewed. Articles which did not relate to the management of symptoms in adult renal populations and those which described management of symptoms yet thought to be less relevant in the last days of life were excluded (eg. renal osteodystrophy, renal anaemia, renal hypertension). An independent review of opioid use in advanced CKD[17] was conducted by another member of the expert group, as part of a research study. Findings were subsequently compared.

A summary of the evidence was presented at a National Steering Group meeting. Opinions were given and provisional guidelines discussed. A first draft proposal was written by the author and reviewed individually by each member of the Expert Consensus group. Individual comments and amendments were taken into consideration before a second draft was reviewed. A third draft of the guidelines was presented and circulated to the entire National Steering Group, before finalising a fourth draft by consensus.

Results

Definition of advanced CKD

The UK CKD guidelines 2005 recommend that renal failure be classified into five stages, according to the estimated glomerular filtration rate (eGFR) (Table 1).[18] The eGFR can be calculated using one of two formulae: the Cockcroft and Gault formula[19] or the 4-point or 6-point Modification of Diet in Renal Disease (MDRD) formula.[20] These formulae correlate to kidney function much more accurately than serum creatinine level, which does not always give an accurate reflection of underlying kidney function because its production is associated with the patient's muscle mass, age, sex, ethnicity and diet. However, we should be aware that all drug product recommendations are based on creatinine clearance, not eGFRs. The MDRD formula is less accurate in significant weight loss, so this must be remembered in those patients with severe cachexia.

Which patients should be on the Renal LCP?

The first decision was to define at what level of renal impairment the Renal LCP Guidelines should be applied. At CKD Stages 4 and 5, drug metabolism is often significantly altered and the risk of drug toxicity may increase in this group of patients. Therefore, the Expert Consensus group agreed that the Renal LCP should be for those

Table 1 Stages of CKD (UK CKD Guidelines, 2005)

Stage	eGFR	Description
1	>90 mL/min	Normal renal function
2[a]	60–89 mL/min	Mildly reduced renal function
3	30–59 mL/min	Moderately reduced renal function
4	15–29 mL/min	Severely reduced renal function
5	<15 mL/min	Very severe or end-stage renal failure

eGFR, estimated glomerular filtration rate.
[a]To fulfil a diagnosis of CKD 2, the patient must have a structural abnormality of the kidneys and/or haematuria or proteinuria in addition to an eGFR 60–90 mL/min.

patients who are in the last days of life, who have an estimated eGFR equal to or below 30 mL/min, correlating to stage 4 or 5 CKD.

The Expert Consensus group also determined that the Renal LCP should be used for patients, who have been identified as being in their last days of life. Often these patients have recently discontinued dialysis and remain conscious and able to swallow medications.

Symptoms in the last days of life in advanced CKD

The guidelines for the generic LCP were originally developed for patients dying of cancer. The prescribing guidelines concentrate on achieving good symptom control for symptoms common in patients dying of cancer: nausea, terminal agitation and restlessness, dyspnoea, respiratory tract secretions and pain.

The common belief is that a uraemic death is relatively symptom-free; however, the evidence does not support this. A recent systematic review of the literature has shown that symptom prevalence is high in dialysis patients,[21] and prospective work reveals that patients with conservatively managed ESRD have a symptom burden similar to patients with terminal cancer or end-stage heart failure.[22] Common symptoms include pain, fatigue, dyspnoea and anxiety. Few studies focus specifically on symptoms at the end-of-life; those that do suggest that although most patients appear to have a 'good death', a significant minority continue to experience these distressing symptoms.[23] The Expert Group agreed that the aim of achieving control of pain, dyspnoea, nausea, respiratory tract secretions and terminal agitation was transferable from the generic LCP to the Renal LCP Guidelines.

Symptom control for the patient dying with advanced CKD

One of the criteria for starting the LCP is that the patient can no longer swallow oral medications. The review of the evidence, therefore, concentrates on drugs which can be given via the subcutaneous route for symptom control. At the point of starting the LCP, the assumption has been made that dialysis will have been stopped, and so we have not mentioned how the pharmacokinetics of the drugs are affected by dialysis.

In the production of the renal prescribing guidelines, the Expert Group had to rely on small pharmacokinetic studies, case-control studies, case reports and case series. Thus, the guidelines are based on Level 3 and 4 evidence.[24] A summary of the conclusions from the evidence are as follows:

Nausea and vomiting

Although there are no head-to-head studies with other antiemetics, expert opinion supports the use of the D_2-receptor antagonist haloperidol as the drug of choice for uraemia-induced nausea.[25] This recommendation is based on clinical experience and that uraemia-induced nausea is thought to be due to stimulation of the chemoreceptor trigger zone, where this drug is active. Its metabolites may accumulate in renal failure, therefore haloperidol at 50% of the normal dose is recommended. Levomepromazine is an alternative antiemetic if symptoms persist. Metoclopramide accumulates leading to an increased risk of extrapyramidal reactions.[26] However, if it is being used effectively, it may continue in a syringe driver at a maximum dose of 30 mg/24 h. Cyclizine may induce hypotension and tachyarrythmias in patients with cardiac disease; since cardiac disease is a common comorbidity in renal patients, cyclizine is, therefore, not recommended.[27]

Box 1: Recommendation

Management of Nausea and Vomiting in the patient dying with Advanced CKD

- Haloperidol is recommended for uraemia-induced nausea at 50% of the normal dose.
- If symptoms persist, levomepromazine is an alternative antiemetic.
- Metoclopramide should be used with caution as there is greater risk of extrapyramidal reactions.
- Cyclizine may induce hypotension and tachyarrythmia and is not recommended.

Respiratory tract secretions

Anticholinergic drugs can reduce respiratory tract secretions in the dying phase. Glycopyrronium or hyoscine butylbromide are recommended for renal patients. There is evidence that glycopyrronium accumulates in renal impairment and that dose reduction is required.[28] The group recommend that half of the normal dose of glycopyrronium is used. Hyoscine hydrobromide crosses the blood–brain barrier and, therefore, may lead to excessive drowsiness or paradoxical agitation in elderly patients with comorbidity.[29] Patients with uraemia are more sensitive to the effects of drugs which cross the blood–brain barrier. Therefore, we do not recommend that hyoscine hydrobromide is used in patients with advanced CKD.

Box 2: Recommendation

Management of Respiratory Tract Secretions in the patient dying with Advanced CKD

- Glycopyrronium or hyoscine butylbromide are recommended for treatment of respiratory tract secretions.
- The dose of glycopyrronium should be reduced to 50% of the normal dose.
- Hyoscine hydrobromide is not recommended because of the risk of excessive drowsiness or paradoxical agitation.

Terminal agitation

The evidence base for optimal drug treatment of terminal agitation is very limited, consequently treatment guidelines are based on expert opinion. In the UK, midazolam is often used if medication is required to relieve agitation in the dying phase. In advanced CKD, more unbound midazolam becomes available and excessive drowsiness may occur.[30] Dose reduction and an increased dosing interval are therefore recommended. If symptoms persist, levomepromazine can be added. When terminal agitation is due to delirium or a psychotic episode, benzodiazepines may make things worse. In these circumstances, haloperidol may be a better drug.

Box 3: Recommendation

Management of Terminal Agitation in the patient dying with Advanced CKD

- Midazolam is recommended if medication is required to relieve agitation in the dying phase. In advanced CKD, more unbound drug becomes available and excessive drowsiness may occur. Dose reduction and an increased dosing interval for midazolam are therefore recommended.
- Levomepromazine can be added if symptoms persist.

Pain and dyspnoea – which opioid?

Drug management of pain and dyspnoea includes use of opioids, which are often given by continuous subcutaneous infusion in the UK. From the available evidence and clinical experience, it is clear that certain opioids can cause significant toxicity in patients with renal failure. Due to the lack of conclusive evidence, reaching a consensus on the recommended opioid in renal failure was a challenge for the group. We summarize the evidence for each opioid in renal failure and illustrate how the Expert Group balanced the evidence with clinical expertise and practical considerations.

Morphine and diamorphine

According to the World Health Organisation, morphine is the opioid of choice in cancer patients with moderate to severe pain.[31] This recommendation is made as morphine is easily available, familiar with clinicians, has established effectiveness and is relatively inexpensive and easy to administer. Diamorphine is a prodrug of morphine and can be given through the parenteral or subcutaneous route. The generic LCP advises that morphine should be used first line for pain control in a patient with cancer who is dying. However, the evidence suggests that if a patient with severe renal impairment is given morphine regularly, there is considerable risk of the patient developing opioid toxicity.

Morphine undergoes hepatic metabolism to morphine-3-glucuronide (55%), morphine-6-glucuronide (M6G) (10%) and normorphine (4%). All of these metabolites are excreted by the kidneys. In patients with normal renal function, approximately 10% of morphine is excreted unchanged by the kidneys.[32]

Severe renal failure is now recognised to have profound effects on the behaviour of the glucuronide metabolites of morphine. Pharmacokinetic studies have shown that the accumulation of the morphine metabolites, in particular M6G, is likely to induce opioid toxicity in patients with severe renal failure.[33–35] M6G is a potent analgesic and central nervous system depressant. There have been several reports of patients with severe renal failure developing significant narcosis, toxic agitation and profound respiratory depression, following the use of morphine. In one particular case, the patient required ventilation and a naloxone infusion for 11 days after the morphine infusion of 10 mg per day was stopped. Investigations found high levels of M6G in the cerebrospinal fluid.[36,37]

In a case-controlled study, 10 patients with renal failure and 10 patients with normal renal function were given a single preoperative dose of 30 mg of morphine, prior to undergoing surgery with spinal anaesthesia.[38] At 4-h intervals, samples of plasma and cerebral spinal fluid (CSF) were taken and analysed. A progressive accumulation of M6G occurred in the patients with renal failure. At 24 h, the concentration of the metabolite in the CSF was at least 15 times higher than in those patients with normal renal function.

M6G crosses the blood–brain barrier slowly and re-equilibrates back into the systemic circulation at a very slow rate. This explains why the effects on the central-nervous system can be prolonged after the morphine has been stopped or removed by dialysis.

Given the evidence, experts recommend that morphine should be avoided in patients with severe renal failure of eGFR <30 mL/min.[17,39,40]

The Expert Consensus group, therefore, do not recommend the use of morphine in patients with advanced CKD. We recognise that sometimes (especially out of the acute hospital setting) alternative opioids are not always available, and therefore recommend that morphine should only be given as a single dose to relieve pain until alternative opioids are accessed. It is suggested that no more than two doses of morphine are given, as if toxicity occurs, it is likely there will be insufficient time for it to be reversed before the patient dies, and hence the patient will experience unnecessary distress.

Oxycodone

Oxycodone is a semisynthetic opioid, used as an alternative to morphine in controlling moderate to severe pain.[41] It undergoes hepatic metabolism principally to oxymorphone and noroxycodone. Of these metabolites, only oxymorphone has been shown to have clinically significant opioid activity in humans. In patients with normal renal

function, this activity is minimal and the opioid agonist effect is believed to be directly related to the oxycodone. However, there is wide interindividual variation, and the studies have not looked at the effect of the metabolites in patients with severe renal failure.[41,42]

Kirvela gave 10 patients with severe renal failure a single dose of oxycodone preoperatively. In comparison to the patients with normal renal function, there was a significant delay in the clearance of the oxycodone. Also, the elimination of the metabolites was prolonged. Interestingly, no adverse effects were reported in either group. One case study reports a patient requiring more than 45 h of a continuous naloxone infusion to reverse oxycodone taken for 8 days whilst on dialysis.[43]

Other than the studies discussed, there is little data on the use of oxycodone in patients with renal failure. Fitzgerald reports anecdotal experience of CNS toxicity and sedation when normal doses of oxycodone are given to patients with severe renal failure.[44] Broadbent suggests using 75% of the normal dose of oxycodone if the creatinine clearance is 10–50 mL/min, and 50% if the creatinine clearance is <10 mL/min, with normal dosing intervals. This is not based on any specific evidence, rather on clinical experience and judgement with regard to the available limited evidence.[45]

Within the Expert Consensus Group, there was some anecdotal experience of using oxycodone successfully in patients with severe renal failure. Those with experience tended to use oxycodone at reduced doses and increased dosing intervals. There was general agreement that the evidence suggests that oxycodone is safer to use in severe renal failure than morphine; however, the evidence is insufficient for it to be strongly recommended.

Oxycodone is, therefore, recommended for use only if alternative opioids are unavailable. If used, dosing intervals should be increased and patients should be monitored closely for opioid toxicity.

Hydromorphone

Hydromorphone is metabolised to hydromorphone-3-glucuronide (H-3-G), which accumulates in renal failure.[46] The activity of H-3-G in humans is not fully established although it is known to be neuroexcitatory in rats.[47] One study looked at pain management in patients with cancer and renal impairment.[48] The study suggests that patients tolerate hydromorphone better than morphine. The study is retrospective in design and the range of creatinine levels suggest (median serum creatinine 127 μmol/L) that patients may have had mild renal failure. Therefore, no firm conclusions can be made regarding the safety and effectiveness of hydromorphone in advanced renal failure. Although there is some anecdotal positive experience of the drug in this setting, due to the limited published evidence, it cannot be recommended.

Fentanyl

Fentanyl is a potent, short-acting synthetic opioid with a relatively short half-life of 1.5–6 h. Because of its low molecular weight and highly lipophillic nature, it is widely used as a transdermal patch for control of moderate to severe pain. However, it can also be given by the subcutaneous route, where a starting dose of 25 μg is approximately equivalent to morphine 2 mg given subcutaneously.[49] Fentanyl is metabolised by the liver to compounds, which are both inactive and nontoxic.[50] The metabolites and approximately 10% of unchanged fentanyl are excreted by the kidneys.

Controversies exist about the influence of renal failure in patients receiving fentanyl. In surgical patients with severe renal failure who were given a single bolus injection of fentanyl, the clearance and distribution of the opioid was similar to surgical patients with normal renal function.[51] This suggests that no dose alteration is required in patients with severe renal failure who are given a single dose of fentanyl. However, there is wide interpatient variability in the pharmacokinetics of fentanyl[52] and a further study has shown that in patients with severe renal failure who are given a single bolus dose of fentanyl, there is a reduction in the clearance of the drug. This may result in respiratory depression.[53] Furthermore, an increase in the half-life of fentanyl (up to 25 h) and distribution volume have been reported in critically ill patients receiving a continuous intravenous infusion of fentanyl.[54]

There is limited evidence for the use of regular or continuous infusions of fentanyl in patients with severe renal failure. Several members of the Expert Consensus Group had considerable experience of using fentanyl in this group of patients. With their experience and in the knowledge that the metabolites are both inactive and nontoxic, the Expert Consensus Group agreed that the evidence suggests that it is safe to use in the last days of life for a patient dying with advanced CKD. However, in the knowledge that accumulation of the parent drug and an increase in half-life may occur if fentanyl is given as a continuous infusion to patients with severe renal failure, it is recommended that patients be closely monitored for signs of opioid toxicity.

Alfentanil

Alfentanil is a very short-acting opioid with an analgesic effect, which lasts between 5 and 10 min. It is chemically related to fentanyl but has a faster onset time and shorter duration of action. This is due to its pharmacokinetic properties of a small distribution volume and a short half-life of 1.5–3 h.[55] Only a small volume of injection is required, when given by continuous subcutaneous infusion, which can be an advantage over fentanyl, when a patient requires high analgesic doses. It undergoes hepatic metabolism by N- and O-dealkylation to inactive, nontoxic metabolites, which are cleared by the kidneys. Only 1% of the parent unchanged drug is excreted by the kidneys.[56]

Pharmacokinetic studies have shown that in patients with renal failure, there is no change in the volume of distribution or the elimination half-life of alfentanil.[57,58] In

the literature, there have been no reports of alfentanil causing adverse effects in patients with severe renal failure. The evidence suggests that alfentanil is safe to use at normal doses in patients with renal failure.

However, alfentanil is unfamiliar to many palliative and renal professionals. It also has a short duration of action making it unsuitable for the titration of opioids in a patient with uncontrolled pain. It is considerably more expensive than fentanyl.

Given the available evidence and these practical considerations the Expert Consensus Group concluded that fentanyl could be recommended as the opioid of choice for the Renal LCP. However, if a patient shows signs of opioid toxicity or large volumes of fentanyl are required, the patient should be switched to alfentanil.

Summary

The complete document 'Guidelines for LCP Drug Prescribing in Advanced Chronic Kidney Disease' is available from the Marie Curie Palliative Care Institute, Liverpool website.[59] The document includes all recommended drug doses and frequencies, as well as an opioid conversion chart. A summary of the recommendations for opioid prescribing for the management of pain and dyspnoea is summarised in Box 4.

Discussion

End-of-life care in patients dying with advanced CKD is an area which is poorly studied; however, from the limited evidence which exists, it appears that patients with advanced CKD suffer similar symptoms to patients with cancer and for an important minority, the suffering continues until death. The generic LCP appears to be transferable to patients dying with advanced CKD and will hopefully enhance end-of-life care for this population of patients and their carers.

Box 4 Opioid Prescribing Guidelines for patients with pain or dyspnoea who are dying with advanced CKD

- Fentanyl by the subcutaneous route is recommended for pain and dyspnoea
- Alfentanil is recommended by continuous infusion if the patient develops signs of toxicity on fentanyl or if the dose of fentanyl exceeds 500 μg per 24 h (due to high volume).
- Oxycodone, hydromorphone, morphine and diamorphine should only be used short-term if alternative opioids are not immediately available
- Morphine or diamorphine should not be given regularly or by continuous infusion

There is a striking lack of evidence for symptom control in patients with renal failure and few studies on how renal impairment affects the pharmacokinetics and pharmacodynamics of the drugs, which we commonly use to control symptoms in the dying phase. When any drug is given to a patient with severe renal failure, it is important to consider how the drug is metabolised, whether or not the metabolites are toxic and how the parent drug and metabolites are excreted. If a proportion of the drug is excreted unchanged by the kidneys, then it is liable to accumulate in severe renal failure leading to toxicity. Likewise, if the metabolites are excreted by the kidneys and the metabolites are active or toxic, the patient is more likely to suffer from drug toxicity or adverse effects.

The Renal LCP Guidelines are based on Level 3 and 4 evidence and expert opinion from within the Consensus Group. The greatest challenge was on making the recommendations for opioid use. Although the evidence is limited, there is a strong suggestion that morphine and diamorphine are likely to cause adverse effects in severe renal impairment. It is recognised that clinicians are more familiar with morphine than the alternative opioids, and one concern was that if morphine is not recommended, patients may not receive adequate analgesia. However, the group agreed that in order to avoid the risk of toxicity it should not be given regularly for a patient dying with severe renal failure.

Although alfentanil seems to be the safest opioid in severe renal impairment, its short-acting nature makes it a poor choice for breakthrough pain relief. It is also unfamiliar to some palliative physicians and even more unfamiliar for nonpalliative professionals. Reaching a consensus on the recommendations for opioid prescribing was, therefore, a balance between the evidence, experience and practical considerations.

Conclusion

The survival of patients with advanced CKD, commencing dialysis, varies depending on age and comorbidity but is as low as 18% for patients aged greater than 75 years, which is lower than for many cancers.[60] Team-working between nephrology and palliative medicine professionals is essential to allow optimum management of these patients. Further research into the symptoms at the end of life for these patients is required and continued studies into the pharmacology of the drugs which we use in the dying phase is necessary to determine how they are affected by renal failure. The LCP provides guidelines based on the best available evidence intended to improve the care of the dying patient with advanced renal disease.

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